Clinical trial results:
The Link between Obesity And Vitamin D in bariatric patients with omega-loop bypass surgery: a randomized controlled, double-blinded clinical supplementation trial - LOAD

Summary

EudraCT number	2013-003546-16
Trial protocol	AT
Global end of trial date	03 June 2016

Results information

Result version number	v1 (current)
This version publication date	12 August 2017
First version publication date	12 August 2017

Trial information

Trial identification

Sponsor protocol code	1.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02092376
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria,
Public contact	Michael Krebs, Klin. Abt. für Endokrinologie & Stoffwechsel, Univ.klinik für Innere Medizin III, 0043 1404004364, maria.luger@meduniwien.ac.at
Scientific contact	Maria Luger, Klin. Abt. für Endokrinologie & Stoffwechsel, Univ.klinik für Innere Medizin III, 0043 1404004364, maria.luger@meduniwien.ac.at

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	03 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test whether administering up to three doses of 100 000 IU vitamin D3 in the first month postoperatively (loading dose), followed by 3420 IU/day (intervention group LMD) in bariatric patients will increase significantly 25-hydroxyvitamin D levels 24 weeks after surgery, compared with a control group receiving placebo, followed by the standard daily doses of 3420 IU/ day (control group ST).

Protection of trial subjects:

The trial subjects were protected by performing anamneses every visit and if necessary forward the patient to specific clinics in our university hospital.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	49
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In- and out-patients of the Obesity Clinics at the Department of Internal Medicine III or the Department of Surgery in the General Hospital of Vienna were recruited between April 2014 and April 2015.

Pre-assignment

Screening details:

After collecting baseline data or screening for in- and exclusion criteria, eligibility was assessed. Bariatric patients with following inclusion criteria were recruited: men and women aged 18–100 years with planned OLGB surgery, serum 25(OH)D concentrations of <75 nmol/L, and body weight <140 kg (due to body weight limitation of the DXA).

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.

Arm type	Experimental
Investigational medicinal product name	Oleovit D3-Tropfen
Investigational medicinal product code	A11CC05
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Loading dose: 100 000 IU of cholecalciferol per dose and up to 3 doses (maximum 300 000 IU) in the first month after gastric bypass surgery
Maintenance dose: 3420 IU per week (over 46 weeks) and starting after loading dose

Arm title	Placebo/control arm

Arm description:

The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.

Arm type	Placebo
Investigational medicinal product name	Oil (medium-chain-Triglyceride)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

The placebo loading dose (without vitamin D) is divided into three administrations and will be given over the first months (the same as treatment arm). After the last placebo loading dose a maintenance dose of 3420 IU per day is given (the same dosage as the treatment arm).

Number of subjects in period 1	Treatment arm	Placebo/control arm
Started	25	25
Completed	25	25

Period 2

Period 2 title	Active/ intervention period (6 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.

Arm type	Experimental
Investigational medicinal product name	Oleovit D3-Tropfen
Investigational medicinal product code	A11CC05
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.

Arm title	Placebo/control arm

Arm description:

The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.

Arm type	Placebo
Investigational medicinal product name	Oil (medium-chain-Triglyceride)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.

Number of subjects in period 2	Treatment arm	Placebo/control arm
Started	25	25
Received allocated intervention	23	23
Completed	21	22
Not completed	4	3
Lost to follow-up	2	1
Protocol deviation	2	2

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description:

50 patients with mean age of 42 (SD 13) years and 80% were female. Mean BMI was 43.8 (4.3) kg/m2 and mean 25-hydroxy vitamin D was 39.0 (16.2) nmol/l.

Reporting group values	Baseline period	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	42		
standard deviation	± 13	-	
Gender categorical Units: Subjects			
Female	40	40	
Male	10	10	

Subject analysis sets

Subject analysis set title	Baseline assessment
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients were analysed.

Subject analysis set title	6-months outcome assessment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary outcome variable 25(OH)D was analyzed according to the intention-to-treat (ITT) principle (including all randomized participants). To handle missing data, the multiple imputation (MI) method was used for the main analysis. Repeated measure analysis of covariance (ANCOVA) using random error (linear mixed model) was used to assess the effect of time and the interaction for changes in parameters between the groups, by using different covariance structure models as appropriate and were adjusted for baseline value, season, age, and sex to supply an unbiased estimate of the mean group difference. Moreover, a post hoc analysis with Bonferroni correction was used.

Reporting group values	Baseline assessment	6-months outcome assessment	
Number of subjects	50	43	
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			
Age continuous Units: years			
arithmetic mean	42	43	
standard deviation	± 13	± 12	
Gender categorical Units: Subjects			
Female	40	40	
Male	10	10	

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description:	
The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.	
Reporting group title	Placebo/control arm
Reporting group description:	
The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.	
Reporting group title	Treatment arm
Reporting group description:	
The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.	
Reporting group title	Placebo/control arm
Reporting group description:	
The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.	
Subject analysis set title	Baseline assessment
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients were analysed.	
Subject analysis set title	6-months outcome assessment
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary outcome variable 25(OH)D was analyzed according to the intention-to-treat (ITT) principle (including all randomized participants). To handle missing data, the multiple imputation (MI) method was used for the main analysis. Repeated measure analysis of covariance (ANCOVA) using random error (linear mixed model) was used to assess the effect of time and the interaction for changes in parameters between the groups, by using different covariance structure models as appropriate and were adjusted for baseline value, season, age, and sex to supply an unbiased estimate of the mean group difference. Moreover, a post hoc analysis with Bonferroni correction was used.	

Primary: 25-hydroxy vitamin D

End point title	25-hydroxy vitamin D
End point description:	
Primary outcome variable was measured at baseline, 0.5, 1, 2, 3, 4, 5, 6 months postoperatively.	
End point type	Primary
End point timeframe:	
6 months after surgery	

End point values	Treatment arm	Placebo/control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[1]	25[2]		
Units: nmol/l				
arithmetic mean (standard deviation)	68.9 (± 21.6)	56.4 (± 22.5)		

Notes:

[1] - ITT

[2] - ITT

Attachments (see zip file)	Primary_outcome.jpg

Statistical analyses

Statistical analysis title	Primary outcome

Statistical analysis description:

The primary outcome variable was analyzed according to the intention-to-treat principle with repeated measure analysis of covariance (ANCOVA) using random error (linear mixed model) to assess the effect of time and the interaction for changes between the groups and were adjusted for age, sex, baseline values, dosing, and season. Moreover, a post hoc analysis with Bonferroni correction was used.

Comparison groups	Treatment arm v Placebo/control arm
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 6 months

Adverse event reporting additional description:

After 2 weeks, 1, 2, 3, 4, 5, 6 month(s) postoperatively any signs or symptoms of vitamin D toxicity or other adverse events, including serious illness or hospitalizations were assessed.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD-10
Dictionary version	2.0

Reporting groups

Reporting group title	Treatment arm

Reporting group description:

The first loading dose of 100,000 IU vitamin D3 (cholecalciferol) was given on day 1 or 2 after surgery, followed by the second (2 weeks) and third administrations (4 weeks postoperatively) if 25(OH)D serum concentration remained below 75 nmol/L. The maximum loading dose for the intervention group was 300,000 IU. After the last loading dose, a maintenance dose of 3420 IU/day (approximately translating to 24,000 IU/week) was given.

Reporting group title	Placebo/control arm

Reporting group description:

The control group received placebo as loading dose and subsequently the maintenance dose, the same way as the intervention group.

Serious adverse events	Treatment arm	Placebo/control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction	Additional description: This SAE occurred before bariatric surgery and before administration of the study medication vitamin D3 (cholecalciferol) at baseline. Therefore it could not be related to the study medication. The patient was allocated to the treatment arm.		
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Liver injury	Additional description: This liver hematoma occurred as a consequence of liver biopsy during surgery and before administration of study medication vitamin D3 at baseline. Therefore it could not be related to the study medication. The patient was in placebo/control arm.		
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
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	Treatment arm	Placebo/control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	19 / 25 (76.00%)	
General disorders and administration site conditions			
Alopecia			
subjects affected / exposed	7 / 25 (28.00%)	5 / 25 (20.00%)	
occurrences (all)	7	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 25 (28.00%)	7 / 25 (28.00%)	
occurrences (all)	7	7	
Vomiting			
subjects affected / exposed	6 / 25 (24.00%)	4 / 25 (16.00%)	
occurrences (all)	6	4	
Reflux			
subjects affected / exposed	4 / 25 (16.00%)	3 / 25 (12.00%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2015	Change of principal investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27837387