Clinical trial results:
Clinical Trial of pharmacokinetics of calcifediol (25OHD3) in women with postmenopausal osteoporosis

Summary

EudraCT number	2015-005303-91
Trial protocol	IT
Global end of trial date	25 September 2019

Results information

Result version number	v1 (current)
This version publication date	30 June 2021
First version publication date	30 June 2021

Trial information

Trial identification

Sponsor protocol code	VIT_D_2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	VIT_D_2015: VIT_D_2015

Notes:

Sponsors

Sponsor organisation name	Azienda Ospedaliera Universitaria Senese
Sponsor organisation address	VIALE MARIO BRACCI 16, Siena, Italy, 53100
Public contact	UOC Medicina Interna 1, Prof. Stefano Gonnelli, Azienda Ospedaliera Universitaria Senese, +39 0577585468, gonnelli@unisi.it
Scientific contact	UOC Medicina Interna 1, Prof. Stefano Gonnelli, Azienda Ospedaliera Universitaria Senese, +39 0577585468, gonnelli@unisi.it

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	29 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2019
Global end of trial reached?	Yes
Global end of trial date	25 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic of 25(OH)D3 in postmenopausal women with osteoporosis treated for 6 months with two different dosages of calcifediol.
To evaluate the efficacy of two different dosages of calcifediol in the achievement of serum levels of 25(OH)D3 higher than 30 ng/ml in women with postmenopausal osteoporosis.

Protection of trial subjects:

Not Applicable

Background therapy:

Not Applicable

Evidence for comparator: -

Actual start date of recruitment	06 April 2017
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	Italy: 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)	35
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolment at department of internal Medicine 1 at Univ. Hosp. Siena (From 04/2017 to 02/2019) Postmenopausal women (amenorrhea) for at least 5 years, Age between 55 and 70 years, Lumbar or femoral T-score ≤ -2.5SD, Plasma levels of 25OHD3 between 10 and 20 ng/ml, Informed consenst signed, Willingness and capacity to adhere to study protocol

Pre-assignment

Screening details:

92 patients were screened, of which 42 excluded for non-compliance with the inclusion criteria
- Postmenopausal women (amenorrhea) for at least 5 years
- Age between 55 and 70 years
- Lumbar or femoral T-score ≤ -2.5 SD
- Plasma levels of 25OHD3 between 10 and 20 ng/ml

Period 1

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

Blinding implementation details:

Not Applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Low dose Arm

Arm description:

Patients will receive 28 drops per week of calcifediol equal to 140 mcg for six months (= 4 drops per day)
Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.

Arm type	Experimental
Investigational medicinal product name	Calcifediol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, suspension
Routes of administration	Oral use

Dosage and administration details:

Patients will receive 28 drops of calcifediol (oral use) per week equal to 140 mcg for six months.

Arm title	High dose Arm

Arm description:

Patients will receive 42 drops per week of calcifediol equal to 210 mcg for six months (= 4 drops per day) Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.

Arm type	Experimental

Investigational medicinal product name	Calcifediol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, suspension
Routes of administration	Oral use

Dosage and administration details:

Patients will receive 42 drops of calcifediol (oral use) per week equal to 210 mcg for six months.

Number of subjects in period 1	Low dose Arm	High dose Arm
Started	25	25
Completed	23	23
Not completed	2	2
Consent withdrawn by subject	1	-
Logistical problems	1	1
Health problems not related to study	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Low dose Arm
Reporting group description:	
Patients will receive 28 drops per week of calcifediol equal to 140 mcg for six months (= 4 drops per day) Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.	
Reporting group title	High dose Arm
Reporting group description:	
Patients will receive 42 drops per week of calcifediol equal to 210 mcg for six months (= 4 drops per day) Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.	

Reporting group values	Low dose Arm	High dose Arm	Total
Number of subjects	25	25	50
Age categorical			
Postmenopausal women 55-70 years			
Units: Subjects			
Adults (18-64 years)	17	18	35
From 65-84 years	8	7	15
Age continuous			
Units: years			
arithmetic mean	62.4	61.6	
standard deviation	± 7.3	± 8.2	-
Gender categorical			
Female			
Units: Subjects			
Female	25	25	50
BMD			
Bone mineral density			
Units: gram(s)/square meter			
arithmetic mean	9670	9580	
standard deviation	± 1600	± 1040	-
25OH-Vit. D			
Fasting venous blood sample			
Units: nanogram(s)/millilitre			
arithmetic mean	15.2	16.1	
standard deviation	± 4.8	± 5.1	-
BMI			
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean	26.1	25.5	
standard deviation	± 3.2	± 3.9	-
Serum Calcium			
Units: millimole(s)/litre			

arithmetic mean	2.33	2.35	
standard deviation	± 0.1	± 0.1	-
Calciuria			
Units: milligram(s)/24 hours			
arithmetic mean	158.0	149.5	
standard deviation	± 70.4	± 69.0	-
1-25OHD2			
Units: nanogram(s)/millilitre			
arithmetic mean	0.045	0.045	
standard deviation	± 0.012	± 0.011	-
Handgrip			
Units: kilogram(s)			
arithmetic mean	18.5	18.3	
standard deviation	± 4.7	± 4.8	-

Subject analysis sets

Subject analysis set title	Analysys Anova
Subject analysis set type	Per protocol

Subject analysis set description:

For the comparison between the two independent groups of the study, the T-test will be used, or, if necessary, the non-parametric equivalent of the Mann-Whitney test

Reporting group values	Analysys Anova		
Number of subjects	46		
Age categorical			
Postmenopausal women 55-70 years			
Units: Subjects			
Adults (18-64 years)	33		
From 65-84 years	13		
Age continuous			
Units: years			
arithmetic mean	61.8		
standard deviation	± 7.9		
Gender categorical			
Female			
Units: Subjects			
Female	46		
BMD			
Bone mineral density			
Units: gram(s)/square meter			
arithmetic mean	9650		
standard deviation	± 1390		
25OH-Vit. D			
Fasting venous blood sample			
Units: nanogram(s)/millilitre			
arithmetic mean	15.7		
standard deviation	± 6.3		
BMI			
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean	25.9		

standard deviation	± 4.2		
Serum Calcium Units: millimole(s)/litre			
arithmetic mean	2.35		
standard deviation	± 0.1		
Calciuria Units: milligram(s)/24 hours			
arithmetic mean	155.1		
standard deviation	± 79.4		
1-25OHD2 Units: nanogram(s)/millilitre			
arithmetic mean	0.045		
standard deviation	± 0.014		
Handgrip Units: kilogram(s)			
arithmetic mean	18.3		
standard deviation	± 4.5		

End points

End points reporting groups

Reporting group title	Low dose Arm

Reporting group description:

Patients will receive 28 drops per week of calcifediol equal to 140 mcg for six months (= 4 drops per day)
Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.

Reporting group title	High dose Arm

Reporting group description:

Patients will receive 42 drops per week of calcifediol equal to 210 mcg for six months (= 4 drops per day) Treatment will last 6 months. After 7, 14, 21, 30, 90 and 180 days of therapy respectively, the patient will undergo the scheduled check-ups with evaluation Calcemia, phosphorus, creatinine, calcium, phosphaturia, creatininuria (24 hour urine), total alkaline phosphatase and bone , serum cross-laps, 25OHD, 1.25 (OH) 2D3 and PTH. Muscle strength evaluation by Hand-grip.

Subject analysis set title	Analysys Anova
Subject analysis set type	Per protocol

Subject analysis set description:

For the comparison between the two independent groups of the study, the T-test will be used, or, if necessary, the non-parametric equivalent of the Mann-Whitney test

Primary: 25OHD3 serum levels at 180 days

End point title	25OHD3 serum levels at 180 days

End point description:

25OHD3 serum levels at 180 days

End point type	Primary

End point timeframe:

25OHD3 serum levels at baseline and 15, 30, 60, 90, 180 days

End point values	Low dose Arm	High dose Arm	Analysys Anova	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	23	46	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	53.9 (± 26.8)	67.0 (± 25.0)	61.8 (± 26.0)	

Statistical analyses

Statistical analysis title	Analysis Anova 25OHD3 serum levels at 180 days

Statistical analysis description:

Evaluation also at 15, 30, 60, 90 days

Comparison groups	Low dose Arm v High dose Arm

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Secondary: 1-25OHD2 serum levels at 180 days

End point title	1-25OHD2 serum levels at 180 days
End point description: 1-25OHD2 serum levels at 180 days	
End point type	Secondary
End point timeframe: 1-25OHD2 serum levels at baseline and 15, 30, 60, 90, 180 days	

End point values	Low dose Arm	High dose Arm	Analysys Anova	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	23	46	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	0.047 (± 0.031)	0.054 (± 0.014)	0.051 (± 0.020)	

Statistical analyses

Statistical analysis title	Analysis 1-25OHD2 Anova at 180 days
Comparison groups	High dose Arm v Low dose Arm
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Secondary: Calcemia at 180 days

End point title	Calcemia at 180 days
End point description: Serum Total Calcium at 180 days	
End point type	Secondary
End point timeframe: Serum Total Calcium at baseline and 15, 30, 60, 90, 180 days	

End point values	Low dose Arm	High dose Arm	Analysys Anova	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	23	46	
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	2.43 (± 0.08)	2.4 (± 0.08)	2.38 (± 0.08)	

Statistical analyses

Statistical analysis title	Analysis Calcemia Anova at 180 days
Statistical analysis description: Evaluation also at 15, 30, 60, 90 days	
Comparison groups	Low dose Arm v High dose Arm
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Secondary: Calciuria at 180 days

End point title	Calciuria at 180 days
End point description: Calciuria at 180 days	
End point type	Secondary
End point timeframe: Calciuria at baseline and 30, 60, 90, 180 days	

End point values	Low dose Arm	High dose Arm	Analysys Anova	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	23	46	
Units: milligram(s)/24 hours				
arithmetic mean (standard deviation)	203 (± 125)	220 (± 112.2)	213 (± 117)	

Statistical analyses

Statistical analysis title	Calciuria at 180 days Anova Test
Statistical analysis description: Evaluation also at 15, 30, 60, 90 days	

Comparison groups	High dose Arm v Low dose Arm
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Secondary: Muscle strenght (Handgrip) at 180 days

End point title	Muscle strenght (Handgrip) at 180 days
End point description: Muscle strenght (Handgrip) at 180 days	
End point type	Secondary
End point timeframe: Muscle strenght (Handgrip) at baseline and 30, 60, 90, 180 days	

End point values	Low dose Arm	High dose Arm	Analysys Anova	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23	23	46	
Units: kilogram(s)				
arithmetic mean (standard deviation)	19.6 (± 4.6)	21.0 (± 5.5)	20.2 (± 4.9)	

Statistical analyses

Statistical analysis title	Handgrip Anova Analysis at 180 days
Statistical analysis description: Evaluation also at 15, 30, 60, 90 days	
Comparison groups	High dose Arm v Low dose Arm
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Evaluation of side effects at all visits	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Low dose arm
Reporting group description: -	
Reporting group title	High dose arm
Reporting group description: -	

Serious adverse events	Low dose arm	High dose arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Low dose arm	High dose arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/33506314