Clinical trial results:
BEST-D (Biochemical efficacy and safety trial of vitamin D): a dose-finding trial assessing biochemical and vascular effects of high dose vitamin D

Summary

EudraCT number	2011-005763-24
Trial protocol	GB
Global end of trial date	10 March 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	CTSUBEST-D

Additional study identifiers

ISRCTN number	ISRCTN07034656
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTSU, Richard Doll Building, Old Road Campus, Oxford, United Kingdom, OX3 7LF
Public contact	Professor Jane Armitage, University of Oxford, 44 (0)1865 743743, jane.armitage@ndph.ox.ac.uk
Scientific contact	Professor Jane Armitage, University of Oxford, 44 (0)1865 743743, jane.armitage@ndph.ox.ac.uk

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	15 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2014
Global end of trial reached?	Yes
Global end of trial date	10 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to determine the optimal safe and effective dose of vitamin D to test in a large scale trial in older people and compare the biochemical effects on blood levels of vitamin D and parathyroid hormone of 100 mcg or 50 mcg or placebo when administered daily for one year.

Protection of trial subjects:

The participants were provided with a 24-hour Freefone number (0800 585323), should they wish to discuss trial-related medical problems outside of the normal working hours.

Background therapy:

None

Evidence for comparator:

Osteoporosis causes substantial morbidity and mortality in older people, but whether chronic insufficiency of vitamin D is a reversible determinant of osteoporosis and related risk of fractures is controversial. Observational studies indicate that low plasma levels of 25-hydroxyvitamin D [25(OH)D] are associated with higher risks of fractures and with vascular and non-vascular mortality, but it is unclear if these associations are causal. Randomized trials assessing the effects on fracture and other health outcomes have generally failed to demonstrate beneficial effects of vitamin D supplementation. However, few such trials have used sufficient doses of vitamin D3 to achieve and maintain what might be considered optimum plasma levels of 25(OH)D.
Although controversial, the available evidence suggests that the optimum plasma levels of 25(OH)D may be around 75 to 90 nmol/L. First, parathyroid hormone (PTH) levels are linearly and inversely associated with plasma 25(OH)D levels until such levels reach about 75 nmol/L. Second, prospective observational studies indicate that the risks of vascular and non-vascular mortality are lowest at plasma 25(OH)D levels of around 90 nmol/L. Thirdly, mean peak plasma 25(OH)D levels at the end of summer in young British adults are also about 90 nmol/L. At plasma 25(OH)D levels below a cut-off point of about 75 nmol/L, the average increase in 25(OH)D per 10 µg of additional vitamin D3 has been estimated to be about 7–10 nmol/L. Hence, from a typical level of 25(OH)D of 55 (SD 26) nmol/L found in older UK adults, a dose of vitamin D3 of at least 50 µg (2000 IU), and possibly as much as 100 µg (4000 IU), may be required to achieve and maintain blood levels >90 nmol/L throughout the year in most people in the UK.

Actual start date of recruitment	30 April 2012
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	United Kingdom: 305
Worldwide total number of subjects	305
EEA total number of subjects	305

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)	0
From 65 to 84 years	292
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

932 subjects were invited to participate, of which 313 (33%) agreed to have a randomization visit from the study nurse and 305 were successfully randomized between 24 September 2012 and 14 March 2013.

Pre-assignment

Screening details:

Eight participants visited were not randomized (6 declined and 2 were ineligible) and 619 declined or ignored the invitation to participate.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The trial was placebo-controlled. The data analyst remained blinded until the Statistical Analysis Plan was finalised.

Arms

Are arms mutually exclusive?	Yes
Arm title	100 µg D3

Arm description:

Vitamin D3 100 µg (4000 IU) daily

Arm type	Active comparator
Investigational medicinal product name	Vitamin D3
Investigational medicinal product code	
Other name	Cholecalciferol
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

100µg (4000 IU) daily

Arm title	50 µg D3

Arm description:

Vitamin D3 50 µg (2000 IU) daily

Arm type	Active comparator
Investigational medicinal product name	Vitamin D3
Investigational medicinal product code	
Other name	Cholecalciferol
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

50µg (2000 IU) daily

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Participants were provided with a pair of treatment bottles. Bottles were labeled with participant details to enable identification. Each treatment bottle contained a 7-month supply of capsules containing either vitamin D3 (50µg) or placebo. Participants were asked to take one capsule from the each of the labelled bottles daily. If they forgot to take the two capsules at the usual time, they could still take them later the same day. However, if they missed a whole day or more, they should have continued with their daily dose from the day they restarted.

Number of subjects in period 1	100 µg D3	50 µg D3	Placebo
Started	102	102	101
6 month visit	98	100	98
12 month visit	97	98	95
Completed	97	98	95
Not completed	5	4	6
Adverse event, serious fatal	-	-	3
Consent withdrawn by subject	3	4	2
Lost to follow-up	1	-	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	100 µg D3
Reporting group description: Vitamin D3 100 µg (4000 IU) daily	
Reporting group title	50 µg D3
Reporting group description: Vitamin D3 50 µg (2000 IU) daily	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	100 µg D3	50 µg D3	Placebo
Number of subjects	102	102	101
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	71	72	72
standard deviation	± 6	± 6	± 6
Gender categorical Units: Subjects			
Female	50	51	49
Male	52	51	52
Current smoker Units: Subjects			
Yes	7	7	7
No	95	95	94
Prior heart disease			
Defined as heart attack, angina or heart failure.			
Units: Subjects			
Yes	20	11	11
No	82	91	90
Prior stroke/TIA Units: Subjects			
Yes	5	8	6
No	97	94	95

Prior hypertension Units: Subjects			
Yes	40	44	35
No	62	58	66
Prior diabetes Units: Subjects			
Yes	9	9	9
No	93	93	92
Prior fracture (ever) Units: Subjects			
Yes	31	30	30
No	71	72	71
Any fall in the past 6 months Units: Subjects			
Yes	13	15	12
No	89	87	89
Taking any antihypertensive Units: Subjects			
Yes	50	52	46
No	52	50	55
Taking statin Units: Subjects			
Yes	32	29	23
No	70	73	78
Taking any antithrombotic Units: Subjects			
Yes	20	23	18
No	82	79	83
Taking vitamin D (<=400 IU/day) Units: Subjects			
Yes	12	10	13
No	90	92	88
Taking calcium Units: Subjects			
Yes	4	1	4
No	98	101	97
Any muscle aches/pains Units: Subjects			
Yes	43	35	38
No	59	67	63
Any joint aches/pains Units: Subjects			
Yes	66	66	64
No	36	36	37
Albumin-corrected calcium			
Number of subjects with albumin-corrected calcium concentration >2.55 mmol/L at randomization			
Units: Subjects			
Yes	5	1	2
No	97	101	99

Height			
Units: cm			
arithmetic mean	168	168	167
standard deviation	± 10	± 10	± 10
Weight			
Units: kg			
arithmetic mean	77	78	79
standard deviation	± 17	± 15	± 15
Body mass index			
Units: kg/m²			
arithmetic mean	27	27	28
standard deviation	± 5	± 4	± 5
Grip strength			
Average of best of 3 left handed tests and best of 3 right handed tests.			
Units: kg			
arithmetic mean	25	25	25
standard deviation	± 11	± 11	± 11
Systolic blood pressure			
Units: mm Hg			
arithmetic mean	132	132	129
standard deviation	± 22	± 17	± 18
Diastolic blood pressure			
Units: mm Hg			
arithmetic mean	77	77	76
standard deviation	± 11	± 10	± 12
Physical activity rating			
Self rated			
Units: Scale of 1-10			
arithmetic mean	6.5	6.2	6.5
standard deviation	± 2	± 2	± 2
Plasma 25(OH)D			
Units: nmol/L			
arithmetic mean	49	55	47
standard deviation	± 15	± 23	± 15
Total cholesterol			
Units: mmol/L			
arithmetic mean	5.4	5.2	5.2
standard deviation	± 1	± 1.2	± 1.2
HDL cholesterol			
Units: mmol/L			
arithmetic mean	1.5	1.5	1.4
standard deviation	± 0.4	± 0.4	± 0.4
LDL cholesterol			
Units: mmol/L			
arithmetic mean	3	2.8	2.8
standard deviation	± 0.8	± 0.9	± 0.8
Triglycerides			
Units: mmol/L			
arithmetic mean	1.6	1.7	1.6
standard deviation	± 0.8	± 1	± 0.9
Apolipoprotein A1			
Units: mg/dL			

arithmetic mean	140	137	136
standard deviation	± 21	± 19	± 21
Apolipoprotein B			
Units: mg/dL			
arithmetic mean	97	92	94
standard deviation	± 21	± 23	± 23
Albumin			
Units: g/L			
arithmetic mean	40	40	40
standard deviation	± 2	± 3	± 3
Creatinine			
Units: µmol/L			
arithmetic mean	79	80	78
standard deviation	± 21	± 23	± 18
eGFR			
Units: mL/min/1.73m²			
arithmetic mean	77	76	78
standard deviation	± 15	± 14	± 13
Alkaline phosphatase			
Units: IU/L			
arithmetic mean	60	64	63
standard deviation	± 17	± 19	± 27
Albumin-corrected calcium			
Units: mmol/L			
arithmetic mean	2.3	2.3	2.3
standard deviation	± 0.1	± 0.1	± 0.1
Phosphate			
Units: mmol/L			
arithmetic mean	1.1	1	1
standard deviation	± 0.2	± 0.2	± 0.1
Ln intact parathyroid hormone			
Units: ln pmol/L			
arithmetic mean	1.37	1.35	1.32
standard deviation	± 0.5	± 0.38	± 0.42
Ln NT-proBNP			
Units: ln pg/mL			
arithmetic mean	6.19	6.19	5.89
standard deviation	± 1.38	± 1.02	± 1.1
Dietary calcium			
Units: mg/day			
arithmetic mean	724	695	713
standard deviation	± 287	± 292	± 302

Reporting group values	Total		
Number of subjects	305		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	150		
Male	155		
Current smoker			
Units: Subjects			
Yes	21		
No	284		
Prior heart disease			
Defined as heart attack, angina or heart failure.			
Units: Subjects			
Yes	42		
No	263		
Prior stroke/TIA			
Units: Subjects			
Yes	19		
No	286		
Prior hypertension			
Units: Subjects			
Yes	119		
No	186		
Prior diabetes			
Units: Subjects			
Yes	27		
No	278		
Prior fracture (ever)			
Units: Subjects			
Yes	91		
No	214		
Any fall in the past 6 months			
Units: Subjects			
Yes	40		
No	265		
Taking any antihypertensive			
Units: Subjects			
Yes	148		
No	157		
Taking statin			
Units: Subjects			
Yes	84		

No	221		
Taking any antithrombotic Units: Subjects			
Yes	61		
No	244		
Taking vitamin D (<=400 IU/day) Units: Subjects			
Yes	35		
No	270		
Taking calcium Units: Subjects			
Yes	9		
No	296		
Any muscle aches/pains Units: Subjects			
Yes	116		
No	189		
Any joint aches/pains Units: Subjects			
Yes	196		
No	109		
Albumin-corrected calcium			
Number of subjects with albumin-corrected calcium concentration >2.55 mmol/L at randomization			
Units: Subjects			
Yes	8		
No	297		
Height Units: cm arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Body mass index Units: kg/m² arithmetic mean standard deviation	- -		
Grip strength			
Average of best of 3 left handed tests and best of 3 right handed tests.			
Units: kg arithmetic mean standard deviation	- -		
Systolic blood pressure Units: mm Hg arithmetic mean standard deviation	- -		
Diastolic blood pressure Units: mm Hg arithmetic mean standard deviation	- -		

Physical activity rating			
Self rated			
Units: Scale of 1-10 arithmetic mean standard deviation	- -		
Plasma 25(OH)D Units: nmol/L arithmetic mean standard deviation	- -		
Total cholesterol Units: mmol/L arithmetic mean standard deviation	- -		
HDL cholesterol Units: mmol/L arithmetic mean standard deviation	- -		
LDL cholesterol Units: mmol/L arithmetic mean standard deviation	- -		
Triglycerides Units: mmol/L arithmetic mean standard deviation	- -		
Apolipoprotein A1 Units: mg/dL arithmetic mean standard deviation	- -		
Apolipoprotein B Units: mg/dL arithmetic mean standard deviation	- -		
Albumin Units: g/L arithmetic mean standard deviation	- -		
Creatinine Units: µmol/L arithmetic mean standard deviation	- -		
eGFR Units: mL/min/1.73m² arithmetic mean standard deviation	- -		
Alkaline phosphatase Units: IU/L arithmetic mean standard deviation	- -		
Albumin-corrected calcium Units: mmol/L arithmetic mean			

standard deviation	-		
Phosphate Units: mmol/L arithmetic mean standard deviation	-		
Ln intact parathyroid hormone Units: ln pmol/L arithmetic mean standard deviation	-		
Ln NT-proBNP Units: ln pg/mL arithmetic mean standard deviation	-		
Dietary calcium Units: mg/day arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	100 µg D3
Reporting group description: Vitamin D3 100 µg (4000 IU) daily	
Reporting group title	50 µg D3
Reporting group description: Vitamin D3 50 µg (2000 IU) daily	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	Randomized
Subject analysis set type	Full analysis
Subject analysis set description: All randomized subjects	
Subject analysis set title	Selected for one month visit
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects selected for the one month visit	
Subject analysis set title	Had 1 month visit
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who attended the 1 month visit.	
Subject analysis set title	Had 6 month visit
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who attended the 6 month visit	
Subject analysis set title	Had 12 month visit
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who attended the 12 month visit	

Primary: Plasma 25(OH)D concentration at scheduled study end

End point title	Plasma 25(OH)D concentration at scheduled study end
End point description: Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Primary
End point timeframe: 12 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: nmol/L				
arithmetic mean (standard error)	137 (± 2.4)	102 (± 2.4)	53 (± 2.4)	

Statistical analyses

Statistical analysis title	Plasma 25(OH)D at scheduled study end
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	ANCOVA

Notes:

[1] - Test for difference

Primary: Proportion of subjects with a 25(OH)D concentration >90 nmol/L at scheduled study end

End point title	Proportion of subjects with a 25(OH)D concentration >90 nmol/L at scheduled study end

End point description:

End point type	Primary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	90	71	1	

Statistical analyses

Statistical analysis title	Proportion with 25(OH)D >90 nmol/L at study end
Comparison groups	100 µg D3 v 50 µg D3

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0016
Method	Chi-squared

Notes:

[2] - Test for difference

Secondary: Plasma 25(OH)D concentration at 1 month

End point title	Plasma 25(OH)D concentration at 1 month

End point description:

Adjusted for baseline values with missing data imputed using multiple imputation.
Only among those selected for the 1 month sample.

End point type	Secondary

End point timeframe:

1 month

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	35	33	
Units: nmol/L				
arithmetic mean (standard error)	81 (± 1.9)	69 (± 1.8)	49 (± 1.9)	

Statistical analyses

Statistical analysis title	Plasma 25(OH)D concentration at 1 month
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	ANCOVA

Notes:

[3] - Test for difference

Statistical analysis title	Plasma 25(OH)D concentration at 1 month
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	ANCOVA

Notes:

[4] - Test for difference

Statistical analysis title	Plasma 25(OH)D concentration at 1 month
Comparison groups	50 µg D3 v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	ANCOVA

Notes:
[5] - Test for difference

Secondary: Plasma 25(OH)D concentration at 6 months

End point title	Plasma 25(OH)D concentration at 6 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation

End point type	Secondary

End point timeframe:
6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: nmol/L				
arithmetic mean (standard error)	126 (± 2.4)	97 (± 2.4)	55 (± 2.4)	

Statistical analyses

Statistical analysis title	Plasma 25(OH)D concentration at 6 months
Comparison groups	50 µg D3 v 100 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	ANCOVA

Notes:
[6] - Test for difference

Statistical analysis title	Plasma 25(OH)D concentration at 6 months
Comparison groups	100 µg D3 v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	ANCOVA

Notes:

[7] - Test for difference

Statistical analysis title	Plasma 25(OH)D concentration at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	ANCOVA

Notes:

[8] - Test for difference

Secondary: Proportion of subjects with a 25(OH)D concentration >90 nmol/L at 6 months

End point title	Proportion of subjects with a 25(OH)D concentration >90 nmol/L at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	88	65	2	

Statistical analyses

Statistical analysis title	Proportion with 25(OH)D >90 nmol/L at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0003
Method	Chi-squared

Notes:

[9] - Test for difference

Statistical analysis title	Proportion with 25(OH)D >90 nmol/L at 6 months
Comparison groups	Placebo v 100 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Chi-squared

Notes:

[10] - Test for difference

Statistical analysis title	Proportion with 25(OH)D >90 nmol/L at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	Chi-squared

Notes:

[11] - Test for difference

Secondary: Proportion of participants with PTH levels suppressed into the normal range at 6 months

End point title	Proportion of participants with PTH levels suppressed into the normal range at 6 months

End point description:

Proportion of participants with a PTH concentration in the reference interval (1.1-6.8 pmol/L)

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	91	97	89	

Statistical analyses

Statistical analysis title	Proportion with PTH in normal range at 6 months
Comparison groups	50 µg D3 v 100 µg D3

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.13
Method	Chi-squared

Notes:

[12] - Test for difference

Statistical analysis title	Proportion with PTH in normal range at 6 months
Comparison groups	Placebo v 100 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.81
Method	Chi-squared

Notes:

[13] - Test for difference

Statistical analysis title	Proportion with PTH in normal range at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.08
Method	Chi-squared

Notes:

[14] - Test for difference

Secondary: Proportion of participants with PTH levels suppressed into the normal range at 12 months

End point title	Proportion of participants with PTH levels suppressed into the normal range at 12 months

End point description:

Proportion of participants with a PTH concentration in the reference interval (1.1-6.8 pmol/L)

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	93	97	88	

Statistical analyses

Statistical analysis title	Proportion with PTH in normal range at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.27
Method	Chi-squared

Notes:

[15] - Test for difference

Statistical analysis title	Proportion with PTH in normal range at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.36
Method	Chi-squared

Notes:

[16] - Test for difference

Statistical analysis title	Proportion with PTH in normal range at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.05
Method	Chi-squared

Notes:

[17] - Test for difference

Secondary: Proportion of participants with calcium levels above the normal range at 6 months

End point title	Proportion of participants with calcium levels above the normal range at 6 months

End point description:

Proportion of participants with an albumin-corrected calcium concentration above the reference interval (2.15-2.55 mmol/L)

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	5	1	0	

Statistical analyses

Statistical analysis title	Proportion with calcium above normal range at 6 mo
Comparison groups	50 µg D3 v 100 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.14
Method	Chi-squared

Notes:

[18] - Test for difference

Statistical analysis title	Proportion with calcium above normal range at 6 mo
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.07
Method	Chi-squared

Notes:

[19] - Test for difference

Statistical analysis title	Proportion with calcium above normal range at 6 mo
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 1
Method	Chi-squared

Notes:

[20] - Test for difference

Secondary: Proportion of participants with calcium levels above the normal range at 12 months

End point title	Proportion of participants with calcium levels above the normal range at 12 months

End point description:

Proportion of participants with an albumin-corrected calcium concentration above the reference interval (2.15-2.55 mmol/L)

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: Subjects	4	1	1	

Statistical analyses

Statistical analysis title	Proportion with calcium above normal range at 12 m
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.21
Method	Chi-squared

Notes:

[21] - Test for difference

Statistical analysis title	Proportion with calcium above normal range at 12 m
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.21
Method	Chi-squared

Notes:

[22] - Test for difference

Statistical analysis title	Proportion with calcium above normal range at 12 m
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.99
Method	Chi-squared

Notes:

[23] - Test for difference

Secondary: Plasma albumin at 6 months

End point title	Plasma albumin at 6 months

End point description:

Mean plasma concentration of albumin (g/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: g/L				
arithmetic mean (standard error)	39.7 (± 0.2)	39.7 (± 0.2)	39.9 (± 0.2)	

Statistical analyses

Statistical analysis title	Plasma albumin at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.91
Method	ANCOVA

Notes:
[24] - Test for difference

Statistical analysis title	Plasma albumin at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.47
Method	ANCOVA

Notes:
[25] - Test for difference

Statistical analysis title	Plasma albumin at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.4
Method	ANCOVA

Notes:
[26] - Test for difference

Secondary: Plasma albumin at 12 months

End point title	Plasma albumin at 12 months

End point description:

Mean plasma concentration of albumin (g/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: g/L				
arithmetic mean (standard error)	40 (± 0.19)	40.1 (± 0.19)	40.6 (± 0.2)	

Statistical analyses

Statistical analysis title	Plasma albumin at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.84
Method	ANCOVA

Notes:

[27] - Test for difference

Statistical analysis title	Plasma albumin at 12 months
Comparison groups	Placebo v 100 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.037
Method	ANCOVA

Notes:

[28] - Test for difference

Statistical analysis title	Plasma albumin at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.06
Method	ANCOVA

Notes:

[29] - Test for difference

Secondary: Plasma phosphate at 6 months	
End point title	Plasma phosphate at 6 months

End point description:

Mean plasma concentration of phosphate (mmol/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	1.08 (± 0.014)	1.04 (± 0.014)	1.06 (± 0.014)	

Statistical analyses

Statistical analysis title	Plasma phosphate at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.09
Method	ANCOVA

Notes:

[30] - Test for difference

Statistical analysis title	Plasma phosphate at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.38
Method	ANCOVA

Notes:

[31] - Test for difference

Statistical analysis title	Plasma phosphate at 6 months
Comparison groups	Placebo v 50 µg D3

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.42
Method	ANCOVA

Notes:

[32] - Test for difference

Secondary: Plasma phosphate at 12 months

End point title	Plasma phosphate at 12 months

End point description:

Mean plasma concentration of phosphate (mmol/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	1.06 (± 0.013)	1.05 (± 0.013)	1.06 (± 0.013)	

Statistical analyses

Statistical analysis title	Plasma phosphate at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.46
Method	ANCOVA

Notes:

[33] - Test for difference

Statistical analysis title	Plasma phosphate at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.71
Method	ANCOVA

Notes:

[34] - Test for difference

Statistical analysis title	Plasma phosphate at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.72
Method	ANCOVA

Notes:

[35] - Test for difference

Secondary: Plasma creatinine at 6 months	
End point title	Plasma creatinine at 6 months

End point description:

Mean plasma concentration of creatinine (ln µmol/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln µmol/L				
arithmetic mean (standard error)	4.36 (± 0.01)	4.35 (± 0.01)	4.34 (± 0.01)	

Statistical analyses

Statistical analysis title	Plasma creatinine at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.54
Method	ANCOVA

Notes:

[36] - Test for difference

Statistical analysis title	Plasma creatinine at 6 months
Comparison groups	100 µg D3 v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.15
Method	ANCOVA

Notes:

[37] - Test for difference

Statistical analysis title	Plasma creatinine at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	= 0.41
Method	ANCOVA

Notes:

[38] - Test for difference

Secondary: Plasma creatinine at 12 months

End point title	Plasma creatinine at 12 months

End point description:

Mean plasma concentration of creatinine (ln µmol/L)
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln µmol/L				
arithmetic mean (standard error)	4.36 (± 0.01)	4.34 (± 0.01)	4.35 (± 0.01)	

Statistical analyses

Statistical analysis title	Plasma creatinine at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.15
Method	ANCOVA

Notes:

[39] - Test for difference

Statistical analysis title	Plasma creatinine at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.21
Method	ANCOVA

Notes:

[40] - Test for difference

Statistical analysis title	Plasma creatinine at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.84
Method	ANCOVA

Notes:

[41] - Test for difference

Secondary: Plasma alkaline phosphatase at 6 months

End point title	Plasma alkaline phosphatase at 6 months

End point description:

Mean plasma concentration of alkaline phosphatase (ln IU/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln IU/L				
arithmetic mean (standard error)	4.04 (± 0.012)	4.06 (± 0.012)	4.08 (± 0.012)	

Statistical analyses

Statistical analysis title	Plasma alkaline phosphatase at 6 months
Comparison groups	100 µg D3 v 50 µg D3

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.46
Method	ANCOVA

Notes:

[42] - Test for difference

Statistical analysis title	Plasma alkaline phosphatase at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.0247
Method	ANCOVA

Notes:

[43] - Test for difference

Statistical analysis title	Plasma alkaline phosphatase at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.13
Method	ANCOVA

Notes:

[44] - Test for difference

Secondary: Plasma alkaline phosphatase at 12 months

End point title	Plasma alkaline phosphatase at 12 months

End point description:

Mean plasma concentration of alkaline phosphatase (ln IU/L).
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln IU/L				
arithmetic mean (standard error)	4.09 (± 0.016)	4.09 (± 0.016)	4.09 (± 0.016)	

Statistical analyses

Statistical analysis title	Plasma alkaline phosphatase at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.98
Method	ANCOVA

Notes:
[45] - Test for difference

Statistical analysis title	Plasma alkaline phosphatase at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.99
Method	ANCOVA

Notes:
[46] - Test for difference

Statistical analysis title	Plasma alkaline phosphatase at 12 months
Comparison groups	50 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 1
Method	ANCOVA

Notes:
[47] - Test for difference

Secondary: Total cholesterol at 12 months

End point title	Total cholesterol at 12 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	5.26 (± 0.063)	5.22 (± 0.064)	5.29 (± 0.063)	

Statistical analyses

Statistical analysis title	Total cholesterol at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.7
Method	ANCOVA

Notes:
[48] - Test for difference

Statistical analysis title	Total cholesterol at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.7
Method	ANCOVA

Notes:
[49] - Test for difference

Statistical analysis title	Total cholesterol at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[50]
P-value	= 0.45
Method	ANCOVA

Notes:
[50] - Test for difference

Secondary: LDL cholesterol at 12 months	
End point title	LDL cholesterol at 12 months
End point description: Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Secondary
End point timeframe: 12 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	2.85 (± 0.05)	2.83 (± 0.05)	2.83 (± 0.05)	

Statistical analyses

Statistical analysis title	LDL cholesterol at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.89
Method	ANCOVA

Notes:
[51] - Test for difference

Statistical analysis title	LDL cholesterol at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.86
Method	ANCOVA

Notes:
[52] - Test for difference

Statistical analysis title	LDL cholesterol at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.97
Method	ANCOVA

Notes:
[53] - Test for difference

Secondary: HDL cholesterol at 12 months	
End point title	HDL cholesterol at 12 months
End point description:	
Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	1.47 (± 0.016)	1.46 (± 0.016)	1.51 (± 0.016)	

Statistical analyses

Statistical analysis title	HDL cholesterol at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.74
Method	ANCOVA

Notes:

[54] - Test for difference

Statistical analysis title	HDL cholesterol at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0.06
Method	ANCOVA

Notes:

[55] - Test for difference

Statistical analysis title	HDL cholesterol at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.0278
Method	ANCOVA

Notes:

[56] - Test for difference

Secondary: Triglycerides at 12 months

End point title	Triglycerides at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmol/L				
arithmetic mean (standard error)	1.7 (± 0.067)	1.72 (± 0.068)	1.66 (± 0.067)	

Statistical analyses

Statistical analysis title	Triglycerides at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.82
Method	ANCOVA

Notes:

[57] - Test for difference

Statistical analysis title	Triglycerides at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	= 0.71
Method	ANCOVA

Notes:

[58] - Test for difference

Statistical analysis title	Triglycerides at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.55
Method	ANCOVA

Notes:

[59] - Test for difference

Secondary: Apolipoprotein A1 at 12 months

End point title	Apolipoprotein A1 at 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mg/dL				
arithmetic mean (standard error)	139 (± 1)	138 (± 1)	142 (± 1)	

Statistical analyses

Statistical analysis title	Apolipoprotein A1 at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	= 0.62
Method	ANCOVA

Notes:
[60] - Test for difference

Statistical analysis title	Apolipoprotein A1 at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.09
Method	ANCOVA

Notes:
[61] - Test for difference

Statistical analysis title	Apolipoprotein A1 at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	= 0.0296
Method	ANCOVA

Notes:
[62] - Test for difference

Secondary: Apolipoprotein B at 12 months

End point title	Apolipoprotein B at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mg/dL				
arithmetic mean (standard error)	94 (± 1.3)	94 (± 1.3)	94 (± 1.3)	

Statistical analyses

Statistical analysis title	Apolipoprotein B at 12 months
Comparison groups	50 µg D3 v 100 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.98
Method	ANCOVA

Notes:

[63] - Test for difference

Statistical analysis title	Apolipoprotein B at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.95
Method	ANCOVA

Notes:

[64] - Test for difference

Statistical analysis title	Apolipoprotein B at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0.97
Method	ANCOVA

Notes:

[65] - Test for difference

Secondary: hsCRP at 6 months	
End point title	hsCRP at 6 months
End point description: Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Secondary
End point timeframe: 6 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln mg/dL				
arithmetic mean (standard error)	4.9 (± 0.007)	4.91 (± 0.007)	4.92 (± 0.007)	

Statistical analyses

Statistical analysis title	hsCRP at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	= 0.23
Method	ANCOVA

Notes:
[66] - Test for difference

Statistical analysis title	hsCRP at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0.16
Method	ANCOVA

Notes:
[67] - Test for difference

Statistical analysis title	hsCRP at 6 months
Comparison groups	Placebo v 50 µg D3

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	= 0.82
Method	ANCOVA

Notes:
[68] - Test for difference

Secondary: hsCRP at 12 months

End point title	hsCRP at 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln mg/dL				
arithmetic mean (standard error)	4.92 (± 0.007)	4.92 (± 0.007)	4.94 (± 0.007)	

Statistical analyses

Statistical analysis title	hsCRP at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.63
Method	ANCOVA

Notes:
[69] - Test for difference

Statistical analysis title	hsCRP at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[70]
P-value	= 0.08
Method	ANCOVA

Notes:
[70] - Test for difference

Statistical analysis title	hsCRP at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.0259
Method	ANCOVA

Notes:
[71] - Test for difference

Secondary: NT-proBNP at 12 months

End point title	NT-proBNP at 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: ln pg/mL				
arithmetic mean (standard error)	6.17 (± 0.056)	6.04 (± 0.057)	6.23 (± 0.058)	

Statistical analyses

Statistical analysis title	NT-proBNP at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[72]
P-value	= 0.11
Method	ANCOVA

Notes:
[72] - Test for difference

Statistical analysis title	NT-proBNP at 12 months
Comparison groups	100 µg D3 v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.52
Method	ANCOVA

Notes:
[73] - Test for difference

Statistical analysis title	NT-proBNP at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.0281
Method	ANCOVA

Notes:
[74] - Test for difference

Secondary: Systolic blood pressure at 6 months

End point title	Systolic blood pressure at 6 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmHg				
arithmetic mean (standard error)	129.7 (± 1.31)	129.9 (± 1.36)	127.8 (± 1.44)	

Statistical analyses

Statistical analysis title	Systolic blood pressure at 6 months
Comparison groups	50 µg D3 v 100 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	= 0.9
Method	ANCOVA

Notes:
[75] - Test for difference

Statistical analysis title	Systolic blood pressure at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[76]
P-value	= 0.34
Method	ANCOVA

Notes:
[76] - Test for difference

Statistical analysis title	Systolic blood pressure at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.29
Method	ANCOVA

Notes:
[77] - Test for difference

Secondary: Systolic blood pressure at 12 months

End point title	Systolic blood pressure at 12 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmHg				
arithmetic mean (standard error)	132.5 (± 1.43)	131.8 (± 1.51)	131.8 (± 1.51)	

Statistical analyses

Statistical analysis title	Systolic blood pressure at 12 months
Comparison groups	100 µg D3 v 50 µg D3

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[78]
P-value	= 0.73
Method	ANCOVA

Notes:
[78] - Test for difference

Statistical analysis title	Systolic blood pressure at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.71
Method	ANCOVA

Notes:
[79] - Test for difference

Statistical analysis title	Systolic blood pressure at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[80]
P-value	= 0.98
Method	ANCOVA

Notes:
[80] - Test for difference

Secondary: Diastolic blood pressure at 6 months

End point title	Diastolic blood pressure at 6 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation

End point type	Secondary

End point timeframe:
6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmHg				
arithmetic mean (standard error)	75.9 (± 0.91)	76.5 (± 0.95)	75.5 (± 1.02)	

Statistical analyses

Statistical analysis title	Diastolic blood pressure at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.63
Method	ANCOVA

Notes:
[81] - Test for difference

Statistical analysis title	Diastolic blood pressure at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[82]
P-value	= 0.81
Method	ANCOVA

Notes:
[82] - Test for difference

Statistical analysis title	Diastolic blood pressure at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.49
Method	ANCOVA

Notes:
[83] - Test for difference

Secondary: Diastolic blood pressure at 12 months	
End point title	Diastolic blood pressure at 12 months
End point description: Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Secondary
End point timeframe: 12 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: mmHg				
arithmetic mean (standard error)	77.2 (± 0.89)	77 (± 0.94)	76.6 (± 0.96)	

Statistical analyses

Statistical analysis title	Diastolic blood pressure at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[84]
P-value	= 0.92
Method	ANCOVA

Notes:
[84] - Test for difference

Statistical analysis title	Diastolic blood pressure at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[85]
P-value	= 0.65
Method	ANCOVA

Notes:
[85] - Test for difference

Statistical analysis title	Diastolic blood pressure at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[86]
P-value	= 0.73
Method	ANCOVA

Notes:
[86] - Test for difference

Secondary: Heart rate at 6 months

End point title	Heart rate at 6 months

End point description:
Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: beats/min				
arithmetic mean (standard error)	64.9 (± 0.81)	65.3 (± 0.85)	66.7 (± 0.92)	

Statistical analyses

Statistical analysis title	Heart rate at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	= 0.71
Method	ANCOVA

Notes:
[87] - Test for difference

Statistical analysis title	Heart rate at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[88]
P-value	= 0.14
Method	ANCOVA

Notes:
[88] - Test for difference

Statistical analysis title	Heart rate at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	= 0.27
Method	ANCOVA

Notes:
[89] - Test for difference

Secondary: Heart rate at 12 months	
End point title	Heart rate at 12 months
End point description:	
Adjusted for baseline values with missing data imputed using multiple imputation.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: beats/min				
arithmetic mean (standard error)	66 (± 0.84)	66.4 (± 0.87)	67 (± 0.87)	

Statistical analyses

Statistical analysis title	Heart rate at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[90]
P-value	= 0.72
Method	ANCOVA

Notes:

[90] - Test for difference

Statistical analysis title	Heart rate at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[91]
P-value	= 0.4
Method	ANCOVA

Notes:

[91] - Test for difference

Statistical analysis title	Heart rate at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[92]
P-value	= 0.64
Method	ANCOVA

Notes:

[92] - Test for difference

Secondary: Pulse trace stiffness index at 6 months

End point title	Pulse trace stiffness index at 6 months

End point description:

Adjusted for baseline values with missing data imputed using multiple imputation

End point type	Secondary

End point timeframe:

6 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: m/s				
arithmetic mean (standard error)	9.6 (± 0.25)	9.6 (± 0.24)	9.5 (± 0.24)	

Statistical analyses

Statistical analysis title	Pulse trace stiffness index at 6 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[93]
P-value	= 0.83
Method	ANCOVA

Notes:

[93] - Test for difference

Statistical analysis title	Pulse trace stiffness index at 6 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[94]
P-value	= 0.7
Method	ANCOVA

Notes:

[94] - Test for difference

Statistical analysis title	Pulse trace stiffness index at 6 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[95]
P-value	= 0.85
Method	ANCOVA

Notes:

[95] - Test for difference

Secondary: Pulse trace stiffness index at 12 months

End point title	Pulse trace stiffness index at 12 months

End point description:

Adjusted for baseline values with missing data imputed using multiple imputation.

End point type	Secondary

End point timeframe:
12 months

End point values	100 µg D3	50 µg D3	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	102	101	
Units: m/s				
arithmetic mean (standard error)	9.4 (± 0.28)	9.4 (± 0.27)	9.5 (± 0.36)	

Statistical analyses

Statistical analysis title	Pulse trace stiffness index at 12 months
Comparison groups	100 µg D3 v 50 µg D3
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[96]
P-value	= 0.96
Method	ANCOVA

Notes:
[96] - Test for difference

Statistical analysis title	Pulse trace stiffness index at 12 months
Comparison groups	100 µg D3 v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[97]
P-value	= 0.94
Method	ANCOVA

Notes:
[97] - Test for difference

Statistical analysis title	Pulse trace stiffness index at 12 months
Comparison groups	Placebo v 50 µg D3
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[98]
P-value	= 0.98
Method	ANCOVA

Notes:
[98] - Test for difference

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 months	
Adverse event reporting additional description:	
All serious adverse events were reported on the electronic case report form, but only those non-serious adverse events that were thought to be related to the study treatment and resulted in the participant stopping treatment were reported.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14

Reporting groups	
Reporting group title	100 µg D3
Reporting group description:	
Randomised to vitamin D3 100 µg (4000 IU) daily	
Reporting group title	50 µg D3
Reporting group description:	
Randomised to vitamin D3 50 µg (2000 IU) daily	
Reporting group title	Placebo
Reporting group description:	
Randomised to placebo	

Serious adverse events	100 µg D3	50 µg D3	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 102 (28.43%)	30 / 102 (29.41%)	25 / 101 (24.75%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastric cancer			

subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant respiratory tract neoplasm			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple myeloma			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	2 / 102 (1.96%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour malignant			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 102 (0.00%)	2 / 102 (1.96%)	3 / 101 (2.97%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			

subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Dupuytren's contracture operation			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye operation			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	3 / 101 (2.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 102 (0.00%)	2 / 102 (1.96%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroidectomy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral bladder resection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Arthroscopy			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 102 (0.00%)	2 / 102 (1.96%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	2 / 102 (1.96%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 102 (0.00%)	2 / 102 (1.96%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspepsia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	2 / 102 (1.96%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	2 / 102 (1.96%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 102 (0.98%)	1 / 102 (0.98%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	2 / 102 (1.96%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	100 µg D3	50 µg D3	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 102 (8.82%)	8 / 102 (7.84%)	8 / 101 (7.92%)
Investigations			
Cystoscopy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences (all)	0	0	1
Vascular test			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Lymphoedema			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences (all)	0	1	0
Uveitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	0 / 101 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 102 (0.98%)	0 / 102 (0.00%)	0 / 101 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 102 (0.00%)	1 / 102 (0.98%)	1 / 101 (0.99%)
occurrences (all)	0	1	1
Infections and infestations			
Genitourinary tract infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 102 (0.00%)	1 / 101 (0.99%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	8 / 102 (7.84%)	4 / 102 (3.92%)	4 / 101 (3.96%)
occurrences (all)	8	4	4

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/25721698