Clinical trial results:
Optimising Vitamin D Status in Older People: A Randomised Controlled Trial of Vitamin D Supplementation

Summary

EudraCT number	2011-004890-10
Trial protocol	GB
Global end of trial date	05 June 2014

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016
Summary attachment (see zip file)	test (Final report for EudraCT version 1.0.doc)

Trial information

Trial identification

Sponsor protocol code	5907

Additional study identifiers

ISRCTN number	ISRCTN35648481
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 12/NE/0050

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1, Regent Point, Regent Farm Road , Gosforth, Newcastle Upon Tyne,, United Kingdom, NE3 3HD
Public contact	Newcastle University , Dr Terry J. Aspray , 0044 191 223 1160, t.j.aspray@newcastle.ac.uk
Scientific contact	Newcastle University , Dr Terry J. Aspray , 0044 191 223 1160, t.j.aspray@newcastle.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	19 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2014
Global end of trial reached?	Yes
Global end of trial date	05 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: We aim to establish the effects of three doses of vitamin D supplement, given for 12 months on the change in bone mineral density (BMD) to indicate a beneficial effect on bone health.

Protection of trial subjects:

No actions required

Background therapy:

No background therapy, ambulant, community dwelling men and women aged 70 years and above

Evidence for comparator:

N/A

Actual start date of recruitment	08 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 379
Worldwide total number of subjects	379
EEA total number of subjects	379

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	367
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Participants were recruited through General Practices participating in the Primary Care Research Network – Northern and Yorkshire (PCRN-NY). Invitation letters were sent to potential recruits, identified from the GP age-sex registers.

Pre-assignment

Screening details:

A member of the research team contacted the participant by telephone to ensured that the participant understood the study, answered any questions the participant had and confirmed eligibility. Subsequently scheduled a first study visit to provide informed consent, a screening safety blood sample to confirm eligibility and safety to take part.

Pre-assignment period milestones

Number of subjects started	379
Number of subjects completed	374

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 5

Period 1

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

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web based system. Patients were randomised in a 1:1:1 ratio to vitamin D 12,000 IU, 24,000 IU or 48,000 IU (Figure 1).A computer-generated allocation list of random permuted blocks was used to appropriate allocation. No unblinding was required during the study, and all code break envelopes were present at the study pharmacy close-out visit.

Arms

Are arms mutually exclusive?	Yes
Arm title	12,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	24,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	48,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 2.4 ml Vigantol oil once a month over the 12 month period.

Number of subjects in period 1[1]	12,000 IU	24,000 IU	48,000 IU
Started	122	124	128
Completed	122	124	128

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2 participants were randomised at screening visit but were found to be ineligible later during the visit and thus were withdrawn. 3 Participants changed their mind during baseline visit and withdrew

Period 2

Period 2 title	0 - 3 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web based system. Patients were randomised in a 1:1:1 ratio to vitamin D 12,000 IU, 24,000 IU or 48,000 IU (Figure 1).A computer-generated allocation list of random permuted blocks was used to appropriate allocation. No unblinding was required during the study, and all code break envelopes were present at the study pharmacy close-out visit.

Arms

Are arms mutually exclusive?	Yes

Arm title	12,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	24,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	48,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 2.4 ml Vigantol oil once a month over the 12 month period.

Number of subjects in period 2	12,000 IU	24,000 IU	48,000 IU
Started	122	124	128
Completed	121	122	124
Not completed	1	2	4
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	1	-	1

Lost to follow-up	-	-	1
Protocol deviation	-	-	1

Period 3

Period 3 title	3 - 6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web based system. Patients were randomised in a 1:1:1 ratio to vitamin D 12,000 IU, 24,000 IU or 48,000 IU (Figure 1).A computer-generated allocation list of random permuted blocks was used to appropriate allocation. No unblinding was required during the study, and all code break envelopes were present at the study pharmacy close-out visit.

Arms

Are arms mutually exclusive?	Yes
Arm title	12,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	24,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	48,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 2.4 ml Vigantol oil once a month over the 12 month period.

Number of subjects in period 3	12,000 IU	24,000 IU	48,000 IU
Started	121	122	124
Completed	118	117	121
Not completed	3	5	3
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	1	1	2
Adverse event, non-fatal	1	2	1
Protocol deviation	-	1	-

Period 4

Period 4 title	6 - 9 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web based system. Patients were randomised in a 1:1:1 ratio to vitamin D 12,000 IU, 24,000 IU or 48,000 IU (Figure 1).A computer-generated allocation list of random permuted blocks was used to appropriate allocation. No unblinding was required during the study, and all code break envelopes were present at the study pharmacy close-out visit.

Arms

Are arms mutually exclusive?	Yes

Arm title	12,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	24,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	48,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 2.4 ml Vigantol oil once a month over the 12 month period.

Number of subjects in period 4	12,000 IU	24,000 IU	48,000 IU
Started	118	117	121
Completed	113	116	117
Not completed	5	1	4
Consent withdrawn by subject	2	-	3
Adverse event, non-fatal	3	1	1

Period 5

Period 5 title	9 - 12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web based system. Patients were randomised in a 1:1:1 ratio to vitamin D 12,000 IU, 24,000 IU or 48,000 IU (Figure 1).A computer-generated allocation list of random permuted blocks was used to appropriate allocation. No unblinding was required during the study, and all code break envelopes were present at the study pharmacy close-out visit.

Arms

Are arms mutually exclusive?	Yes
Arm title	12,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	24,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D

Arm type	Experimental
Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 0.6 ml Vigantol and 1.8 ml Miglyol oil once a month over the 12 month period.

Arm title	48,000 IU

Arm description:

Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D

Arm type	Experimental

Investigational medicinal product name	Vigantol®
Investigational medicinal product code	200106 or EMD 28162
Other name	Vigantol Oel
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The vitamin D3 preparation was a liquid, containing 20,000 IU/ml of vitamin D3 (Vigantol) which was mixed with Miglyol oil, which contains no vitamin D3. Both will be provided by MODE Pharma, UK. Participants in this arm received 2.4 ml Vigantol oil once a month over the 12 month period.

Number of subjects in period 5	12,000 IU	24,000 IU	48,000 IU
Started	113	116	117
Completed	113	114	116
Not completed	0	2	1
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	

Reporting group values	12,000 IU	24,000 IU	48,000 IU
Number of subjects	122	124	128
Age categorical Units: Subjects			
From 65-84 years	118	119	122
85 years and over	4	5	6
Age continuous			
Averga			
Units: years			
arithmetic mean	74.6	75	75.4
standard deviation	± 3.9	± 4.3	± 4.4
Gender categorical Units: Subjects			
Male	57	59	65
Female	65	65	63
BMD			
Bone Mineral Density at HIP (DEXA Scan)			
Units: g/cm2			
arithmetic mean	0.98	0.987	0.973
standard deviation	± 0.155	± 0.179	± 0.187
250HD			
Vitamin D as plasma 25OHD			
Units: nm/L			
arithmetic mean	41.38	39.67	38.87
standard deviation	± 19.99	± 20.64	± 19.72
fnBMD			
Femoral neck bone mineral density			
Units: g/cm2			
arithmetic mean	0.898	0.915	0.892
standard deviation	± 0.138	± 0.154	± 0.163
PTH			
Parathyroid hormone			
Units: g/ml			
arithmetic mean	48.28	47.49	49.96
standard deviation	± 25.66	± 23.38	± 21.27
CTX			

C-terminal telopeptide (CTX),			
Units: ng/ml			
arithmetic mean	0.41	0.41	0.4
standard deviation	± 0.17	± 0.19	± 0.19
bone ALP			
bone specific alkaline phosphatase (bone ALP)			
Units: g/L			
arithmetic mean	10.28	10.82	9.99
standard deviation	± 3.72	± 3.79	± 3.19
P1NP			
N-terminal propeptide of procollagen type I (P1NP)			
Units: ug/L			
arithmetic mean	41.15	39.26	39.37
standard deviation	± 18.22	± 15.55	± 16.16
Weight			
in Kg			
Units: kg			
arithmetic mean	73.87	77.21	76.11
standard deviation	± 11.93	± 14.53	± 14.23
Height			
measures in cm			
Units: cm			
arithmetic mean	167.22	167.09	167.39
standard deviation	± 8.07	± 9.86	± 10.01
BMI			
derrived			
Units: kg/m2			
arithmetic mean	26.4	27.56	27.08
standard deviation	± 3.66	± 4.12	± 3.97
Fat mass			
Units: kg			
arithmetic mean	23.94	25.49	24.91
standard deviation	± 8.48	± 8.24	± 8.31
Free fat mass			
Units: kg			
arithmetic mean	49.87	51.66	50.67
standard deviation	± 8.96	± 10.71	± 10.86

Reporting group values	Total		
Number of subjects	374		
Age categorical			
Units: Subjects			
From 65-84 years	359		
85 years and over	15		
Age continuous			
Averga			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Male	181		
Female	193		
BMD			
Bone Mineral Density at HIP (DEXA Scan)			
Units: g/cm2 arithmetic mean standard deviation	- -		
250HD			
Vitamin D as plasma 25OHD			
Units: nm/L arithmetic mean standard deviation	- -		
fnBMD			
Femoral neck bone mineral density			
Units: g/cm2 arithmetic mean standard deviation	- -		
PTH			
Parathyroid hormone			
Units: g/ml arithmetic mean standard deviation	- -		
CTX			
C-terminal telopeptide (CTX),			
Units: ng/ml arithmetic mean standard deviation	- -		
bone ALP			
bone specific alkaline phosphatase (bone ALP)			
Units: g/L arithmetic mean standard deviation	- -		
P1NP			
N-terminal propeptide of procollagen type I (P1NP)			
Units: ug/L arithmetic mean standard deviation	- -		
Weight			
in Kg			
Units: kg arithmetic mean standard deviation	- -		
Height			
measures in cm			
Units: cm arithmetic mean standard deviation	- -		
BMI			
derrived			
Units: kg/m2			

arithmetic mean standard deviation	- 		
Fat mass Units: kg arithmetic mean standard deviation	- 		
Free fat mass Units: kg arithmetic mean standard deviation	- 		

Subject analysis sets	
Subject analysis set title	End of Study
Subject analysis set type	Intention-to-treat

Subject analysis set description:

See protocol for details

http://www.ncbi.nlm.nih.gov/pubmed/24041337

Reporting group values	End of Study		
Number of subjects	374		
Age categorical Units: Subjects			
From 65-84 years 85 years and over			
Age continuous			
Averga			
Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Male Female	181 193		
BMD			
Bone Mineral Density at HIP (DEXA Scan)			
Units: g/cm2 arithmetic mean standard deviation	 ±		
250HD			
Vitamin D as plasma 25OHD			
Units: nm/L arithmetic mean standard deviation	 ±		
fnBMD			
Femoral neck bone mineral density			
Units: g/cm2 arithmetic mean standard deviation	 ±		
PTH			
Parathyroid hormone			

Units: g/ml arithmetic mean standard deviation	±		
CTX			
C-terminal telopeptide (CTX),			
Units: ng/ml arithmetic mean standard deviation	±		
bone ALP			
bone specific alkaline phosphatase (bone ALP)			
Units: g/L arithmetic mean standard deviation	±		
P1NP			
N-terminal propeptide of procollagen type I (P1NP)			
Units: ug/L arithmetic mean standard deviation	±		
Weight			
in Kg			
Units: kg arithmetic mean standard deviation	±		
Height			
measures in cm			
Units: cm arithmetic mean standard deviation	±		
BMI			
derrived			
Units: kg/m2 arithmetic mean standard deviation	±		
Fat mass Units: kg arithmetic mean standard deviation	±		
Free fat mass Units: kg arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	
Subject analysis set title	End of Study
Subject analysis set type	Intention-to-treat

Subject analysis set description:

See protocol for details

http://www.ncbi.nlm.nih.gov/pubmed/24041337

Primary: Change in BMD

End point title	Change in BMD

End point description:

Bone Minderal Density at HIP (DEXA Scan)
The difference in BMD between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Primary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109[1]	106[2]	112[3]	
Units: g/cm2				
arithmetic mean (standard deviation)	-0.001 (± 0.013)	-0.003 (± 0.018)	-0.005 (± 0.016)	

Notes:

[1] - Data not available for all subjects

[2] - Data not available for all subjects

[3] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in BMD from baseline to 12 months

Statistical analysis description:

To compare the response in the three treatment groups while allowing for the effects of baseline covariates. Baseline BMD at hip, parathyroid hormone in plasma and plasma concentration of 25OHD, lean mass, fat mass estimated glomerular filtration rate (GFR) will be included amongst those under consideration in addition to baseline FRAX score, measures of kidney function, weight and height, gender and age. The inclusion of interaction terms will also be explored.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.0535 [4]
Method	ANCOVA

Notes:

[4] - Final model adjusted for baseline bmd, gender, age, weight and height

Secondary: Change in 250HD

End point title	Change in 250HD

End point description:

Vitamin D as plasma 25OHD
The difference in 25OHD between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 Months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112[5]	113[6]	113[7]	
Units: nm/L				
arithmetic mean (standard deviation)	14.27 (± 12.63)	25.32 (± 18.02)	40.58 (± 19.88)	

Notes:

[5] - Data not available for all subjects

[6] - Data not available for all subjects

[7] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in 25OHD from baseline to 12 months

Statistical analysis description:

The ANCOVA model derived for the primary outcome analysis will be used. Consideration will be given to the inclusion of baseline 25OHD in addition if this was not included in the final model for the primary outcome. Significance of this term for inclusion in the final model will be assessed as described previously.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	> 0.001
Method	ANCOVA

Notes:

[8] - Final model adjusted for baseline 25OHD, gender, age, weight and height

Secondary: Change in fnBMD

End point title	Change in fnBMD

End point description:

Femoral-neck bone mineral density
The difference fnBMD between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110[9]	110[10]	111[11]	
Units: g/cm2				
arithmetic mean (standard deviation)	0.002 (± 0.02)	0 (± 0.023)	0.001 (± 0.021)	

Notes:

[9] - Data not available for all subjects

[10] - Data not available for all subjects

[11] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in fnBMD

Statistical analysis description:

The ANCOVA model derived for the primary outcome analysis will be used. Consideration will be given to the inclusion of baseline fnBMD in addition if this was not included in the final model for the primary outcome. Significance of this term for inclusion in the final model will be assessed as described previously.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	> 0.02
Method	ANCOVA

Notes:

[12] - Final model adjusted for baseline fnBMD, baseline PTH, gender, age, weight and height

Secondary: Change in PTH

End point title	Change in PTH

End point description:

Parathyroid hormone
The difference in PTH between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112[13]	113[14]	113[15]	
Units: pg/ml				
arithmetic mean (standard deviation)	-2.92 (± 18.39)	-2.92 (± 18.14)	-10.56 (± 15.4)	

Notes:

[13] - Data not available for all subjects

[14] - Data not available for all subjects

[15] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in PTH

Statistical analysis description:

The ANCOVA model derived for the primary outcome analysis will be used. Consideration will be given to the inclusion of baseline PTH in addition if this was not included in the final model for the primary outcome. Significance of this term for inclusion in the final model will be assessed as described previously.

Comparison groups	24,000 IU v 48,000 IU v 12,000 IU
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	> 0.001
Method	ANCOVA

Notes:

[16] - Final model adjusted for baseline PTH, gender, age, weight and height.

Secondary: Change in CTX

End point title	Change in CTX

End point description:

Change in C-terminal telopeptide
The difference in CTX between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112[17]	113[18]	114[19]	
Units: ng/ml				
arithmetic mean (standard deviation)	-0.046 (± 0.125)	-0.055 (± 124)	-0.031 (± 0.142)	

Notes:

[17] - Data not available for all subjects

[18] - Data not available for all subjects

[19] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in CTX

Statistical analysis description:

An ANCOVA model with change in CTX as dependent variable, independent variables considered, 25OHD, PTH and kidney function at baseline and dietary calcium and vitamin D intake at baseline. Other covariates considered as for primary outcome analysis.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU

Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	> 0.001
Method	ANCOVA

Notes:

[20] - Final model adjusted for baseline CTX, gender, age, weight and height.

Secondary: Change in bone BAP

End point title	Change in bone BAP

End point description:

Change in Bone Alkaline Phosphatase
The difference in BAP between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111[21]	113[22]	114[23]	
Units: ug /L				
arithmetic mean (standard deviation)	0.96 (± 3.398)	0.682 (± 3.761)	0.792 (± 3.82)	

Notes:

[21] - Data not available for all subjects

[22] - Data not available for all subjects

[23] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in bone BAP

Statistical analysis description:

An ANCOVA model with change in BAP as dependent variable, independent variables considered, 25OHD, PTH and kidney function at baseline and dietary calcium and vitamin D intake at baseline. Other covariates considered as for primary outcome analysis.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	> 0.194
Method	ANCOVA

Notes:

[24] - Final model adjusted for baseline BAP, baseline urinary calcium, gender, age, weight and height.

Secondary: Change in P1NP

End point title	Change in P1NP

End point description:

Terminal propeptide of procollagen type 1
The difference in P1NP between baseline and 12 months derived by subtracting baseline from 12m value per individual

End point type	Secondary

End point timeframe:

12 months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112[25]	113[26]	114[27]	
Units: ug/L				
arithmetic mean (standard deviation)	1.129 (± 14.853)	3.367 (± 13.301)	4.031 (± 13.259)	

Notes:

[25] - Data not available for all subjects

[26] - Data not available for all subjects

[27] - Data not available for all subjects

Statistical analyses

Statistical analysis title	Change in P1NP

Statistical analysis description:

An ANCOVA model with change in P1NP as dependent variable, independent variables considered, 25OHD, PTH and kidney function at baseline and dietary calcium and vitamin D intake at baseline. Other covariates considered as for primary outcome analysis.

Comparison groups	12,000 IU v 24,000 IU v 48,000 IU
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	> 0.001
Method	ANCOVA

Notes:

[28] - Final model adjusted for baseline P1NP, baseline urinary calcium/creatinine ratio, gender, age, weight and height.

Secondary: Adverse Evemts

End point title	Adverse Evemts

End point description:

End point type	Secondary

End point timeframe:

12 Months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	124	128	
Units: Adverse Event Occurance				
Mild	296	283	283	
Moderate	131	149	145	
Severe	0	6	3	
Missing	8	2	5	

Attachments (see zip file)	Adverse Events Summary.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Falls

End point title	Falls

End point description:

The number of falls experienced during the study. Expressed as fall rate per 12 months in order to take into account differing durations of study involvement.

End point type	Secondary

End point timeframe:

12 Months

End point values	12,000 IU	24,000 IU	48,000 IU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100[29]	95[30]	97[31]	
Units: Falls per 12 months per patient				
number (not applicable)	48	43	54	

Notes:

[29] - Number of participants with fall data

[30] - Number of participants with fall data

[31] - Number of participants with fall data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Adverse events were reported from first visit until final visit	
Adverse event reporting additional description:	
Throughout the study adverse events were recorded as free text in the medical notes. The adverse events were retrospectively transcribed into the eCRF with best intention for accuracy and completeness. During the transcription no medical dictionary was used in order to avoid bias by retrospectively coding and categorizing these events	
Assessment type	Systematic

Dictionary used	
Dictionary name	Free Text
Dictionary version	NA

Reporting groups	
Reporting group title	12,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 12,000 IU of vitamin D	
Reporting group title	24,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 24,000 IU of vitamin D	
Reporting group title	48,000 IU
Reporting group description:	
Once a month participant received an oral dose of Vigantol® equivalent to 48,000 IU of vitamin D	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Adverse events were reported as secondary outcome and a list off all adverse events is provided there

Serious adverse events	12,000 IU	24,000 IU	48,000 IU
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 122 (11.48%)	9 / 124 (7.26%)	6 / 128 (4.69%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Recurrence of melanoma and cerebral metasteses			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Hepatitis E infection			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrilation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Congestive cardiac faliure			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Congestive heart falure			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Left total anterior circulation infarct with intrecerebral haemorrage post thyromoblysis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Mild posterior circulation stroke			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Transient ischemic attack			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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	2 / 122 (1.64%)	0 / 124 (0.00%)	0 / 128 (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
Chest pain/breathlessness			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Headache and facial swelling			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Headache, postural hypotension and migraine			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Trauma			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
White cell count reduced			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Death Traffic Accident			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Death	Additional description: Unknown cause		
subjects affected / exposed	1 / 122 (0.82%)	1 / 124 (0.81%)	0 / 128 (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
Gastrointestinal disorders			
Ischemic colitis			

subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paracolic abcess			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Respiratory, thoracic and mediastinal disorders			
Exacerbation of asthma			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Possible pulmonary oedema			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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
Right basal pneumonia with pluritis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tightness in chest			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	0 / 128 (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 and connective tissue disorders			
Fractured femur			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Fractured rib			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Right hip joint effusion			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Infections and infestations			
Broncietctasis and lower respiratory tract infection			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 128 (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
Urinary tract infection			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	12,000 IU	24,000 IU	48,000 IU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	0 / 128 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2012	- Peanut allergy removed from exclusion criteria - An optional statement has been added to the informed consent form to allow potential approach of subject for other studies in the future. - Correction to inconsistencies between table and text format of study procedures had been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24041337