



## Clinical trial results:

### Effect of supplementation with vitamin D on the acute bronchitis prevention during the first year of life.

#### Summary

EudraCT number	2012-001152-19
Trial protocol	ES
Global end of trial date	31 December 2016

#### Results information

Result version number	v1 (current)
This version publication date	22 September 2021
First version publication date	22 September 2021

#### Trial information

##### Trial identification

Sponsor protocol code	VitDBR2012
-----------------------	------------

##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, 34 934894865, joaquin.lopez.soriano@vhir.org
Scientific contact	Antonio Moreno-Galdó, VHIR, 34 934893171, amoreno@vhebron.net

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	08 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Check that the administration of a vitamin D dose of 1,000 U / day decreases the percentage of children with acute bronchitis during the first year of life.

Protection of trial subjects:

The study was approved by the Ethics Committees of all the participating centers and the Spanish Agency for Medication and Healthcare Products (Agencia Española de Medicamentos y Productos Sanitarios - AEMPS). Written informed consent was obtained from the infants' parents prior to their inclusion

During the study, a protocol modification approved by the reference Ethics Committee was made in the schedule of intermediate follow-up visits (initially made at 2, 6 and 12 months and changed to visits at 3 and 12 months) and in the evaluation of the levels of calcium used to assess toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Spain: 198
Worldwide total number of subjects	198
EEA total number of subjects	198

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	198
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	0

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

Participants were screened for eligibility in primary care centers and hospitals between November 2013 and December 2015

### Pre-assignment

Screening details:

Eligible participants were healthy full-term newborns with adequate weight for gestational age, fed with breastfeeding or formula feeding. 660 children were initially evaluated, of whom 198 parents accepted their participation and were randomly assigned to the 400 IU/day (n = 94), or 1,000 IU/day groups (n = 104) of vitamin D supplementation

### 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, Carer

Blinding implementation details:

A two phases masking system (phase I – from 0 to 6 months- and phase II- from 6 to 12 months) was designed so children received a final dose of 400 or 1,000 IU/day taking into account the dose they received from feeding with milk formulas in case they received them. Placebo and drug bottles were identical in composition (except for vitamin D), appearance and taste for both groups, and were manufactured by Kern-Pharma Laboratories, (Terrassa, Spain).

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Vitamin D 400 IU/day

Arm description:

Patients received a total of 400 IU of vitamin D either from diet or supplements

Arm type	Active comparator
Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Each participant received at the beginning and at 6 months of the study a kit containing 1 or 2 bottles of the masked assignment taking into account the contribution received through milk formulas in children fed with them. Children could receive supplements of 0, 200 or 400 IU of vitamin D to obtain the final amount of 400 IU/day. Infants receiving artificial formulas were assumed to ingest 400 IU/day of vitamin D for the first 6 months of life (volume of milk ingested 1 liter), and 200 IU/day of vitamin D from 6 to 12 months of life once the complementary feeding has been introduced (volume of milk ingested 500 milliliter).

<b>Arm title</b>	Vitamin D 1000 IU/day
------------------	-----------------------

Arm description:

Patients received a total of 1000 IU of vitamin D either from diet or supplements

Arm type	Experimental
Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

---

**Dosage and administration details:**

Each participant received at the beginning and at 6 months of the study a kit containing 1 or 2 bottles of the masked assignment taking into account the contribution received through milk formulas in children fed with them. Children could receive supplements of 600, 800 or 1,000 IU of vitamin D to obtain the final amount of 1,000 IU/day. Infants receiving artificial formulas were assumed to ingest 400 IU/day of vitamin D for the first 6 months of life (volume of milk ingested 1 liter), and 200 IU/day of vitamin D from 6 to 12 months of life once the complementary feeding has been introduced (volume of milk ingested 500 milliliter).

<b>Number of subjects in period 1</b>	<b>Vitamin D 400 IU/day</b>	<b>Vitamin D 1000 IU/day</b>
Started	94	104
Completed	62	71
Not completed	32	33
Consent withdrawn by subject	4	11
Physician decision	2	-
Lack of compliance	3	3
Lost to follow-up	20	18
Protocol deviation	3	1

## Baseline characteristics

### Reporting groups

Reporting group title	Vitamin D 400 IU/day
-----------------------	----------------------

Reporting group description:

Patients received a total of 400 IU of vitamin D either from diet or supplements

Reporting group title	Vitamin D 1000 IU/day
-----------------------	-----------------------

Reporting group description:

Patients received a total of 1000 IU of vitamin D either from diet or supplements

Reporting group values	Vitamin D 400 IU/day	Vitamin D 1000 IU/day	Total
Number of subjects	94	104	198
Age categorical			
Units: Subjects			
Newborns (0-27 days)	94	104	198
Gender categorical			
Units: Subjects			
Female	46	45	91
Male	48	59	107

## End points

### End points reporting groups

Reporting group title	Vitamin D 400 IU/day
Reporting group description:	
Patients received a total of 400 IU of vitamin D either from diet or supplements	
Reporting group title	Vitamin D 1000 IU/day
Reporting group description:	
Patients received a total of 1000 IU of vitamin D either from diet or supplements	

### Primary: Acute bronchitis

End point title	Acute bronchitis
End point description:	
End point type	Primary
End point timeframe:	
At the end of the study	

End point values	Vitamin D 400 IU/day	Vitamin D 1000 IU/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	92		
Units: Subjects	40	42		

### Statistical analyses

Statistical analysis title	Proportion comparison acute bronchitis
Comparison groups	Vitamin D 400 IU/day v Vitamin D 1000 IU/day
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	11.7

**Secondary: Recurrent bronchitis**

End point title	Recurrent bronchitis
-----------------	----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

At the end of the study

End point values	Vitamin D 400 IU/day	Vitamin D 1000 IU/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	92		
Units: Subjects	8	14		

**Statistical analyses**

<b>Statistical analysis title</b>	Proportion comparison recurrent bronchitis
Comparison groups	Vitamin D 400 IU/day v Vitamin D 1000 IU/day
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	15.2

**Secondary: Acute bronchitis hospitalizations**

End point title	Acute bronchitis hospitalizations
-----------------	-----------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

At the end of the study

End point values	Vitamin D 400 IU/day	Vitamin D 1000 IU/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	92		
Units: Subjects	3	5		

### Statistical analyses

Statistical analysis title	Proportion comparison bronchitis hospitalizations
Comparison groups	Vitamin D 400 IU/day v Vitamin D 1000 IU/day
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	7.9

### Secondary: Upper respiratory tract infections

End point title	Upper respiratory tract infections
End point description:	
End point type	Secondary
End point timeframe:	
At the end of the study	

End point values	Vitamin D 400 IU/day	Vitamin D 1000 IU/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	92		
Units: Subjects	64	70		

### Statistical analyses

Statistical analysis title	Proportion comparison URTI
Statistical analysis description:	
URT = Upper respiratory tract infections	

Comparison groups	Vitamin D 400 IU/day v Vitamin D 1000 IU/day
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.759
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	10.5

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At the end of the study

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.1
--------------------	------

### Reporting groups

Reporting group title	400IU VitD
-----------------------	------------

Reporting group description: -

Reporting group title	1000IU VitD
-----------------------	-------------

Reporting group description: -

Serious adverse events	400IU VitD	1000IU VitD	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 94 (10.64%)	21 / 104 (20.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Surgical intervention			
subjects affected / exposed	0 / 94 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Digestive complications			
subjects affected / exposed	0 / 94 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			

subjects affected / exposed	3 / 94 (3.19%)	7 / 104 (6.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 94 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Whooping cough			
subjects affected / exposed	0 / 94 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary infection			
subjects affected / exposed	0 / 94 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 94 (1.06%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 94 (0.00%)	3 / 104 (2.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	400IU VitD	1000IU VitD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 94 (59.57%)	80 / 104 (76.92%)	
Nervous system disorders			
Seizure	Additional description: Febrile seizure		
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Otitis media			
subjects affected / exposed	11 / 94 (11.70%)	9 / 104 (8.65%)	
occurrences (all)	11	9	
Deafness			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Milk allergy			
subjects affected / exposed	1 / 94 (1.06%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Egg allergy			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	15 / 94 (15.96%)	12 / 104 (11.54%)	
occurrences (all)	15	12	
Gastrointestinal disorders			

Gastroenteritis			
subjects affected / exposed	23 / 94 (24.47%)	27 / 104 (25.96%)	
occurrences (all)	23	27	
Vomiting			
subjects affected / exposed	4 / 94 (4.26%)	5 / 104 (4.81%)	
occurrences (all)	4	5	
Constipation			
subjects affected / exposed	3 / 94 (3.19%)	3 / 104 (2.88%)	
occurrences (all)	3	3	
Colics			
subjects affected / exposed	5 / 94 (5.32%)	5 / 104 (4.81%)	
occurrences (all)	5	5	
Other gastrointestinal problems			
subjects affected / exposed	4 / 94 (4.26%)	5 / 104 (4.81%)	
occurrences (all)	4	5	
Respiratory, thoracic and mediastinal disorders			
Upper airway infection			
subjects affected / exposed	6 / 94 (6.38%)	7 / 104 (6.73%)	
occurrences (all)	6	7	
Whooping cough			
subjects affected / exposed	0 / 94 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	4 / 94 (4.26%)	6 / 104 (5.77%)	
occurrences (all)	4	6	
Nasal obstruction			
subjects affected / exposed	1 / 94 (1.06%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	0 / 94 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Viral exanthematous infection			
subjects affected / exposed	5 / 94 (5.32%)	5 / 104 (4.81%)	
occurrences (all)	5	5	
Dermatitis atopic			

subjects affected / exposed occurrences (all)	11 / 94 (11.70%) 11	20 / 104 (19.23%) 20	
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5	6 / 104 (5.77%) 6	
Dermatitis diaper subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 7	10 / 104 (9.62%) 10	
Other skin lesions subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 6	7 / 104 (6.73%) 7	
Renal and urinary disorders Urinary infection subjects affected / exposed occurrences (all)	2 / 94 (2.13%) 2	3 / 104 (2.88%) 3	
Musculoskeletal and connective tissue disorders Early closure of fontanel subjects affected / exposed occurrences (all)	1 / 94 (1.06%) 1	0 / 104 (0.00%) 0	
Infections and infestations Acute febrile viral infection subjects affected / exposed occurrences (all)	23 / 94 (24.47%) 23	24 / 104 (23.08%) 24	
Localised infection subjects affected / exposed occurrences (all)	7 / 94 (7.45%) 7	7 / 104 (6.73%) 7	
Metabolism and nutrition disorders Failure to thrive subjects affected / exposed occurrences (all)	0 / 94 (0.00%) 0	4 / 104 (3.85%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2013	Enlargement to 16 centers to increase recruitment chances. Approved CEIC 6/09/2013
30 April 2014	1) Authorization for venous blood extraction, instead of capillar, to avoid distress to children. 2)Hypercalciuria levels modification, since they were not originally adjusted to participants ages: calcium/creatinine ratio >0.88 at 2 months age; >0.71 at 6 months age; >0.60 at 12 months age. 3) increase in total blood extraction in children over 6 months of age, from 1 to 1.5 ml. Approved CEIC 6/06/2014
21 July 2014	Second visit modified from 2 to 3 months age, when the urine and blood analytics were done, suppressing the analytics at 6 months. Subject withdraw criteria were modified, from just hypercalciuria, to presence of hypercalcemia or hypercalcemia-associated hypercalciuria. This was suggested by the pharmacovigilance committee since hypercalciuria alone does not allowed to discard a likely toxic effect of Vitamin D, thus being necessary to have also blood levels. Change in the age of the analysis was done to avoid multiple determinations. Approved CEIC 10/10/2014
03 December 2014	Change in blood calcium levels (> 11,3 mg/dl at 3 months, or > 11,4 mg/dl at 12 months), after a publication with reference levels more suitable to the population included in the study, which appeared after writing of the original assay protocol (Roizen JD et al. Determination of reference intervals for serum total calcium in the vitamin D-replete pediatric population. J Clin Endocrinol Metab. 2013;98:E1946-50). Approved CEIC 9/01/2015.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The most significant limitation of the study was the sample size obtained since it was smaller than planned

Notes: