Clinical trial results:
A Double-Blind Randomised Placebo-Controlled Trial of Vitamin D Supplements for Pregnant Women with Low Levels of Vitamin D in Early Pregnancy

Summary

EudraCT number	2007-001716-23
Trial protocol	GB
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	25 October 2019
First version publication date	25 October 2019
Summary attachment (see zip file)	MAVIDOS main results Lancet DE 2016 (MAVIDOS main paper Lancet DE 2016.pdf) MAVIDOS supplementary data Lancet DE 2016 (Cooper_MAVIDOS trial supp data.pdf) MAVIDOS report to age 4 years for MHRA (MAVIDOS MHRA 2019_09_22.pdf)

Trial information

Trial identification

Sponsor protocol code	452622

Additional study identifiers

ISRCTN number	ISRCTN82927713
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust Research & Development
Sponsor organisation address	Tremona Road, Southampton, United Kingdom, SO16 6YD
Public contact	Professor Cyrus Cooper, University Hospitals Southampton NHS Foundation Trust Research and Development, 023 80 777624, cc@mrc.soton.ac.uk
Scientific contact	Professor Cyrus Cooper, University Hospitals Southampton NHS Foundation Trust Research and Development, 023 80 777624, cc@mrc.soton.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	Interim
Date of interim/final analysis	21 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that vitamin D supplementation during pregnancy of women who are have low levels of vitamin D will result in improved neonatal bone mineral content.

The primary completion date encompasses the 4 year followup of the trial.
We have an ongoing grant to follow the children to age 8 years (due to complete in 2021), this has ethics approval under the original ethics number 07/H0502/113.

Protection of trial subjects:

Ethical considerations
The study involves the participants undergoing various procedures with which they may not be familiar. Detailed information sheets are given to the participantsand they have opportunities to discuss any concerns in detail with study personnel. The infant DXA assessments are associated with a low dose of radiation exposure equivalent to 2 days background radiation in Cornwall (UK) or 7 days in other parts of the UK. Data from the Princess Anne Cohort study showed a small excess of atopic asthma in children born to mothers with the highest levels of vitamin D in pregnancy. However, other studies have suggested neutral or negative associations. The dose of vitamin D supplementation has been chosen to bring women just into the normal range, to avoid elevating it to supranormal levels.
For safety reasons, only women with serum 25(OH)D concentrations between 25-100nmol/l could be included in the study.

Reporting of adverse events
A system of adverse event reporting is described in the study protocol (Harvey et al, Trials 2012, 13;13). In summary, any adverse reaction felt in any way to be related to the IMP was immediately reported to the sponsor, followed by a detailed report on the event. The local Principal Investigator decides whether to expedite reports of adverse events felt to be unrelated to the IMP. A record of all serious adverse events is kept in the trial master file regardless of whether reported within 24 hours to the sponsor. The sponsor keeps detailed records of all adverse events relating to a clinical trial which are reported to them by the investigators for the trial. These records may be sent to the licensing authority if required.

Suspected unexpected serious adverse reactions are reported as soon as possible to the MHRA and the relevant ethics/data monitoring committee.

Background therapy:

Women were able to take pregnancy vitamin supplements containing up to 400 IU cholecalciferol.

Evidence for comparator:

The comparators were cholecalciferol 1000 IU versus placebo.
Prior to the study, we did a systematic review of studies relating maternal vitamin 25-hydroxyvitamin D (25[OH]D) concentrations, UVB exposure, dietary vitamin D intake, or use of vitamin D supplements during pregnancy to maternal and offspring health outcomes (Harvey NC, Holroyd C, Ntani G, et al. Vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess 2014; 18: 1–190).
We identified eight observational studies relating maternal gestational vitamin D status to offspring bone mass, all of which were assessed as having a medium to low risk of bias. Of these, five reported a significant positive relation between maternal vitamin D status and offspring bone outcomes, which included whole-body, lumbar, femoral, and tibial bone mineral content (BMC), and whole-body and lumbar spine bone mineral density (BMD). Of the remaining studies, no significant association was reported between maternal vitamin D status and offspring radial and whole-body BMC. Differences in study design did not permit meta-analysis. We identified one small intervention study, judged to be at

high risk of bias, which found no difference in offspring forearm BMC (measured within 5 days of birth) between supplemented and unsupplemented mothers. We subsequently updated the search in August, 2014,
identifying two further observational studies, both judged to have a low to medium risk of bias; one, using the Avon Longitudinal Study of Parents and Children cohort, found no association between maternal 25(OH)D concentrations in pregnancy and offspring bone mass at 9 years. By contrast, the second study, from the Western Australian Pregnancy Cohort (RAINE), documented positive associations between maternal gestational 25(OH)D concentrations and off spring bone mass at 20 years.

Actual start date of recruitment	10 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1134
Worldwide total number of subjects	1134
EEA total number of subjects	1134

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)	1134
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pregnant women were recruited when attending early pregnancy ultrasound screening at three study sites (University Hospital Southampton National Health Service [NHS] Foundation Trust, Southampton, UK; Oxford University Hospitals NHS Trust, Oxford, UK; Sheffield Hospitals NHS Trust [University of Sheffield], Sheffield, UK).

Pre-assignment

Screening details:

Women were eligible if they were older than 18 years, had a singleton pregnancy, had gestation of less than 17 weeks based on last menstrual period and ultrasound measurements, and were aiming to give birth at the local maternity hospital. See Cooper et al, Lancet Diabetes and Endocrinology 2016. 1449 were screened, 1134 randomly assigned.

Period 1

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

Blinding implementation details:

Women were randomly assigned at 14 weeks' gestation to either cholecalciferol 1000 IU/day or matched placebo (Merck KGaA, Darmstadt, Germany).
Packs of study treatment were randomly assigned in a 1:1 ratio by Sharp Clinical Services (Crickhowell, UK; previously DHP-Bilcare) by a computer-generated sequence in randomly permuted blocks of ten, starting randomly midway through the block, dispensed in order by study pharmacist. Both participant and research team were blinded to treatment allocation

Arms

Are arms mutually exclusive?	Yes
Arm title	Cholecalciferol 1000 IU

Arm description:

Women receiving 1000 IU cholecalciferol from 14 weeks gestation to delivery.

Arm type	Active comparator
Investigational medicinal product name	Cholecalciferol 1000 IU /day
Investigational medicinal product code	
Other name	Vitamin D3
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 IU Cholecalciferol, one tablet to be taken orally daily from randomisaton at 14 weeks' gestation (or as soon as possible before 17 weeks' gestation if recruited later) until the day of delivery.

Arm title	Placebo arm

Arm description:

Women receiving placebo tablet

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matched capsule, one to be taken orally daily from 14 weeks gestation to delivery

Number of subjects in period 1	Cholecalciferol 1000 IU	Placebo arm
Started	565	569
Neonatal assessment	416	420
Completed	367	370
Not completed	198	199
Physician decision	4	4
Too busy	4	5
Unwilling/unable to take study drug	27	24
Reason unknown	19	17
Moved away	2	1
Consent withdrawn by subject	37	32
Unusable DXA due to movement artefact	49	50
Adverse event, non-fatal	3	11
Did not attend	-	15
DXA concerns	2	-
Did not attend neonatal assessment	15	-
Miscarriage	1	4
Lost to follow-up	15	18
Refused to attend neonatal followup	8	7
Withdrew after delivery before neonatal DXA	2	5
Protocol deviation	10	6

Baseline characteristics

Reporting groups	
Reporting group title	Cholecalciferol 1000 IU
Reporting group description:	
Women receiving 1000 IU cholecalciferol from 14 weeks gestation to delivery.	
Reporting group title	Placebo arm
Reporting group description:	
Women receiving placebo tablet	

Reporting group values	Cholecalciferol 1000 IU	Placebo arm	Total
Number of subjects	565	569	1134
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	565	569	1134
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age of women at baseline			
Units: years			
arithmetic mean	30.5	30.5	
standard deviation	± 5.2	± 5.2	-
Gender categorical Units: Subjects			
Female	565	569	1134
Male	0	0	0

End points

End points reporting groups

Reporting group title	Cholecalciferol 1000 IU
Reporting group description:	
Women receiving 1000 IU cholecalciferol from 14 weeks gestation to delivery.	
Reporting group title	Placebo arm
Reporting group description:	
Women receiving placebo tablet	

Primary: Child bone mineral content (neonatal)

End point title	Child bone mineral content (neonatal)
End point description:	
Measured by DXA	
End point type	Primary
End point timeframe:	
Within 2 weeks of delivery	

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	327		
Units: gram(s)				
arithmetic mean (confidence interval 95%)	61.6 (60.3 to 62.8)	60.5 (59.3 to 61.7)		

Statistical analyses

Statistical analysis title	T test between groups
Statistical analysis description:	
Hypothesis tests on primary outcome (BMC, grams) between groups of neonates, cholecalciferol vs. placebo	
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.21
Method	t-test, 2-sided

Primary: Child bone mineral density (neonatal)

End point title	Child bone mineral density (neonatal)

End point description: Measured by DXA of neonate	
End point type	Primary
End point timeframe: Within 2 weeks of delivery	

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	327		
Units: g/cm2				
arithmetic mean (confidence interval 95%)	0.203 (0.200 to 0.205)	0.203 (0.200 to 0.205)		

Statistical analyses

Statistical analysis title	Difference in means (BMD)
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.96 [2]
Method	t-test, 2-sided

Notes:

[1] - T test

[2] - There was no difference in neonatal BMD between the groups

Primary: Child lean mass (neonatal)

End point title	Child lean mass (neonatal)
End point description: Lean mass measured by DXA	
End point type	Primary
End point timeframe: Neonatal	

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	327		
Units: grams				
arithmetic mean (confidence interval 95%)	3055 (3008 to 3101)	3014 (2965 to 3062)		

Statistical analyses

Statistical analysis title	T test between groups
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.23
Method	t-test, 2-sided

Secondary: Child bone mineral content (age 4 years)

End point title	Child bone mineral content (age 4 years)

End point description:

MAVIDOS children recruited in the Southampton arm of the trial were followed up at age 4 years. The results comprise a secondary analysis.

End point type	Secondary

End point timeframe:

Four year follow up - median (IQR) age 4.07 years (4.03, 4.15) cholecalciferol 1000 IU/day group; 4.08 years (4.03, 4.16) placebo group.

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	246		
Units: gram(s)				
arithmetic mean (confidence interval 95%)	361.21 (355.70 to 366.72)	356.69 (351.21 to 362.17)		

Statistical analyses

Statistical analysis title	T test between groups

Statistical analysis description:

Differnce in BMC between groups

Comparison groups	Cholecalciferol 1000 IU v Placebo arm

Number of subjects included in analysis	494
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.252
Method	t-test, 2-sided

Secondary: Child bone mineral density (age 4 years)

End point title	Child bone mineral density (age 4 years)

End point description:

End point type	Secondary

End point timeframe:

Child followup of MAVIDOS trial at age 4 years

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	246		
Units: g/cm2				
arithmetic mean (confidence interval 95%)	0.477 (0.472 to 0.481)	0.470 (0.466 to 0.475)		

Statistical analyses

Statistical analysis title	T test between groups
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	494
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.048
Method	t-test, 2-sided

Secondary: Child lean mass (age 4 years)

End point title	Child lean mass (age 4 years)

End point description:

Whole body (less head) lean mass

End point type	Secondary

End point timeframe:

4 year followup DXA scan

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	248		
Units: gram(s)				
arithmetic mean (confidence interval 95%)	9248.25 (9080.01 to 9416.49)	9006.27 (8830.16 to 9182.38)		

Statistical analyses

Statistical analysis title	T test between groups
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	496
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.051
Method	t-test, 2-sided

Other pre-specified: Seasonal analysis of BMC (neonatal)-Winter births	
End point title	Seasonal analysis of BMC (neonatal)-Winter births
End point description: Bone mineral content in winter-born infants (Dec-Feb)	
End point type	Other pre-specified
End point timeframe: Neonatal	

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	64		
Units: gram(s)				
arithmetic mean (standard deviation)	63.0 (± 10.8)	57.5 (± 10.9)		

Statistical analyses

Statistical analysis title	T test between groups
Comparison groups	Cholecalciferol 1000 IU v Placebo arm

Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	t-test, 2-sided

Other pre-specified: Seasonal analysis of BMD (neonatal)-Winter births

End point title	Seasonal analysis of BMD (neonatal)-Winter births

End point description:

End point type	Other pre-specified

End point timeframe:

Neonatal

End point values	Cholecalciferol 1000 IU	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	62		
Units: g/cm2				
arithmetic mean (standard deviation)	0.208 (± 0.024)	0.200 (± 0.019)		

Statistical analyses

Statistical analysis title	T test between groups
Comparison groups	Cholecalciferol 1000 IU v Placebo arm
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.04
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Recruitment (11 weeks-14 weeks) to delivery

Adverse event reporting additional description:

Maternal adverse events

Assessment type	Systematic

Dictionary used

Dictionary name	MAVIDOS dictionary
Dictionary version	1.1

Reporting groups

Reporting group title	Cholecalciferol 1000 IU/day

Reporting group description:

Maternal / neonatal outcomes.

There was 1 intrauterine/neonatal death, no maternal deaths (hence not listed below).

Severe adverse events:
Preterm delivery / premature birth
Instrumental delivery
Severe postpartum haemorrhage
Intrauterine or neonatal death
Congenital abnormalities

Adverse events:
Infection
Nausea/vomiting
Diarrhoea
Abdominal pain
Headache
Hypertension
Hypercalcaemia (>= 2.75 mmol / l at 34 weeks gestation)
Fetal growth retardation

Reporting group title	Placebo group

Reporting group description:

Maternal / neonatal outcomes.

There was 1 intrauterine/neonatal death, no maternal deaths (hence not listed below).

Severe adverse events:
Preterm delivery / premature birth
Instrumental delivery
Severe postpartum haemorrhage
Intrauterine or neonatal death
Congenital abnormalities

Adverse events:
Infection
Nausea/vomiting
Diarrhoea
Abdominal pain
Headache
Hypertension
Hypercalcaemia (>= 2.75 mmol / l at 34 weeks gestation)
Fetal growth retardation

Serious adverse events	Cholecalciferol 1000 IU/day	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	115 / 565 (20.35%)	149 / 569 (26.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Preterm delivery / premature birth			
subjects affected / exposed	16 / 565 (2.83%)	10 / 569 (1.76%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Instrumental delivery			
subjects affected / exposed	25 / 565 (4.42%)	35 / 569 (6.15%)	
occurrences causally related to treatment / all	0 / 25	0 / 35	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe postpartum haemorrhage			
subjects affected / exposed	65 / 565 (11.50%)	96 / 569 (16.87%)	
occurrences causally related to treatment / all	0 / 65	0 / 96	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrauterine or neonatal death			
subjects affected / exposed	1 / 565 (0.18%)	3 / 569 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital abnormalities			
subjects affected / exposed	8 / 565 (1.42%)	5 / 569 (0.88%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cholecalciferol 1000 IU/day	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 565 (11.68%)	71 / 569 (12.48%)	
Cardiac disorders			

Hypertension			
subjects affected / exposed	13 / 565 (2.30%)	15 / 569 (2.64%)	
occurrences (all)	13	15	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 565 (1.42%)	9 / 569 (1.58%)	
occurrences (all)	8	9	
Gastrointestinal disorders			
Nausea / vomiting			
subjects affected / exposed	6 / 565 (1.06%)	7 / 569 (1.23%)	
occurrences (all)	6	7	
Diarrhoea			
subjects affected / exposed	6 / 565 (1.06%)	4 / 569 (0.70%)	
occurrences (all)	6	4	
Abdominal pain			
subjects affected / exposed	16 / 565 (2.83%)	19 / 569 (3.34%)	
occurrences (all)	16	19	
Infections and infestations			
Infection (any)			
subjects affected / exposed	17 / 565 (3.01%)	17 / 569 (2.99%)	
occurrences (all)	17	17	

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

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

Full results of the MAVIDOS trial neonatal followup are published in the Lancet Diabetes and Endocrinology: Lancet Diabetes Endocrinol 2016;
4: 393–402 (link below). Limitations are discussed on p 399-400.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30321476

http://www.ncbi.nlm.nih.gov/pubmed/30669280

http://www.ncbi.nlm.nih.gov/pubmed/27549309

http://www.ncbi.nlm.nih.gov/pubmed/26944421

http://www.ncbi.nlm.nih.gov/pubmed/22314083