Clinical trial results:
The effect of oral Vitamin D supplementation on endothelial function, vascular inflammation, oxidative stress and insulin sensitivity in patients with impaired fasting glucose: A randomised, double blinded, placebo controlled trial

Summary

EudraCT number	2014-002766-73
Trial protocol	GB
Global end of trial date	23 January 2017

Results information

Result version number	v1 (current)
This version publication date	22 June 2022
First version publication date	22 June 2022
Summary attachment (see zip file)	Vitamin-D justification for no results (Vitamin D EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	PHT/2014/44

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Portsmouth Hospitals NHS Trust
Sponsor organisation address	Queen Alexandra Hospital, Portsmouth, United Kingdom, PO6 3LY
Public contact	Linda Harndahl , Portsmouth Hospitals NHS Trust, 0044 2392286236, Research.Office@porthosp.nhs.uk
Scientific contact	Michael Cummings, Portsmouth Hospitals NHS Trust, 0044 2392286000 , michael.cummings@porthosp.nhs.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	09 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2016
Global end of trial reached?	Yes
Global end of trial date	23 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to examine whether Vitamin D3 3,200 IU supplementation in patients with impaired fasting glucose has an effect on: reduction of the VCAM-1 marker (vascular circulating adhesion molecule-1) in blood.

Protection of trial subjects:

The study was conducted in compliance with the Good Clinical Practice (GCP) guidelines, MHRA, REC approved protocol; study site local requirements to ensure the safety of trial participants.
Vitamin D3 is a medication used to treat Vitamin D deficiency in the adults. Uncommon (>1/1000, <1/100) undesirable effects of Vitamin D3 include raised blood calcium levels and raised excretion of calcium in the urine. The dose of Vitamin D3 used in this study is safe and well within the Tolerable Upper Intake Level of 4000 IU/day and extremely unlikely to cause raised calcium levels and complications associated with this. Nonetheless, a system for assessing and reporting of adverse events will be set up to monitor the safety of participants. The exclusion criteria of our study ensure that patients with conditions and on treatments that could increase the risk of Vitamin D side effects are excluded from participation.Vitamin D3 rarely (>1/10 000, <1/1000) causes itching, rash and hives. Vitamin D3 and placebo capsules contain Arachis (peanut) oil that can cause allergic reaction in people with peanut and soya allergy. Patients with peanut and soya allergy will therefore be excluded from participation. All study participants will be made aware of the risks/precautions in a patient information leaflet.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	0

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)	24
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified through routine screening by the clinical team at the Diabetes center. Local GP practices also carried out routine screening and referred eligible participants to the recruiting site.

The search consisted of identifying participants with impaired fasting glucose.

Pre-assignment

Screening details:

Informed consent & participant capacity were assessed by the Principal investigator. Blood samples (11-15ml) will have been taken during the screening visit on participants having fasted overnight before the visit (instructions for fasting were provided on the participant information sheet - PIS). Clinical assessment including ECGs were done.

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

Blinding implementation details:

the identity of the placebo and active drug was appropriately concealed to the investigator team and participants of the study. These were over-encapsulated.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm B

Arm description:

Participants in Arm B received placebo manufactured with appearance identical to the Fultium D3 3,200 IU capsules (Investigational Medicinal Product - IMP). The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Arm type	Placebo
Investigational medicinal product name	Manufactured matched placebo identical to the Fultium D3 3,200 IU capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule orally once a day for 12 weeks (84 days)

Arm title	Arm A

Arm description:

Participants in Arm A received Investigational Medicinal Product (IMP) Fultium D3 3,200 IU capsules. The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Arm type	Experimental

Investigational medicinal product name	Colecalciferol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule containing 3,200 IU of colecalciferol daily

Number of subjects in period 1	Arm B	Arm A
Started	23	23
Completed	23	23

Baseline characteristics

Reporting groups

Reporting group title	Arm B

Reporting group description:

Participants in Arm B received placebo manufactured with appearance identical to the Fultium D3 3,200 IU capsules (Investigational Medicinal Product - IMP). The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Reporting group title	Arm A

Reporting group description:

Participants in Arm A received Investigational Medicinal Product (IMP) Fultium D3 3,200 IU capsules. The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Reporting group values	Arm B	Arm A	Total
Number of subjects	23	23	46
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	61.13	60.56	
standard deviation	± 8.83	± 9.85	-
Gender categorical Units: Subjects			
Female	15	16	31
Male	8	7	15

End points

End points reporting groups

Reporting group title	Arm B

Reporting group description:

Participants in Arm B received placebo manufactured with appearance identical to the Fultium D3 3,200 IU capsules (Investigational Medicinal Product - IMP). The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Reporting group title	Arm A

Reporting group description:

Participants in Arm A received Investigational Medicinal Product (IMP) Fultium D3 3,200 IU capsules. The study IMP for the whole duration of the trial will be dispensed after the 1st study visit by the Pharmacy in Queen Alexandra Hospital, Portsmouth, UK. The IMP was to be taken by the participants orally one capsule orally once a day for 12 weeks (84 days).

Primary: Endothlial activation marker VCAM-1

End point title	Endothlial activation marker VCAM-1

End point description:

The relative change of endothelial activation marker VCAM-1 was the absolute change on logarithmic scale before and after the IMP or placebo.

End point type	Primary

End point timeframe:

12 weeks

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: ng/ml				
number (not applicable)	21	23		

Statistical analyses

Statistical analysis title	Analysis for change in vcam1

Statistical analysis description:

Test for difference in change between vitamin d and placebo arm

Comparison groups	Arm B v Arm A

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.73 [1]
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.0368

Notes:

[1] - Two sided t-test for difference in absolute change between placebo and vitamin-D arms

Secondary: Change in Insulin sensitivity

End point title	Change in Insulin sensitivity

End point description:

Metabolic markers insulin resistance (HOMA-B) was calculated from an average of three measurements of fasting glucose and insulin (RIA).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: NA				
number (not applicable)	23	23		

Statistical analyses

Statistical analysis title	Analysis for change in insulin sensitivity

Statistical analysis description:

Two sided t test for changes in insulin sensitivity

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.64
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.53
upper limit	2.205
Variability estimate	Standard error of the mean
Dispersion value	1.422

Secondary: 8-iso-Prostaglandin F2a

End point title	8-iso-Prostaglandin F2a
End point description: 8-iso-Prostaglandin F2a activity was used as one of oxidative stress markers.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: pg/ml				
number (not applicable)	23	23		

Statistical analyses

Statistical analysis title	Comparison of change in id 8 porstagl between arms
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.267
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	19366.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15412.99
upper limit	54146.28
Variability estimate	Standard error of the mean
Dispersion value	17221.55

Secondary: Cyclic Glycerylmonophosphate

End point title	Cyclic Glycerylmonophosphate

End point description:

Cyclic Glycerylmonophosphate (cGMP) was one of the oxidative stress markers used in the study.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: pmol/ml				
number (not applicable)	21	23		

Statistical analyses

Statistical analysis title	Comparison of change in cGMP between arms
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.053
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.797
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.605
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Total oxidised glutathione ratio

End point title	Total oxidised glutathione ratio

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: NA				
number (not applicable)	23	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Highly sensitive C-reactive protein

End point title	Highly sensitive C-reactive protein
End point description: Highly sensitive C-reactive protein (hsCRP) is one of the markers of vascular inflammation.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: mg/l				
number (not applicable)	23	23		

Statistical analyses

Statistical analysis title	Comparison of change in hscrp between arms
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.63
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.502

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.611
upper limit	2.616
Variability estimate	Standard error of the mean
Dispersion value	1.046

Secondary: Albumin:Creatinine ratio

End point title	Albumin:Creatinine ratio
End point description:	
Albumin: creatinine ratio is one of the markers of vascular inflammation.	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: NA				
number (not applicable)	23	23		

Statistical analyses

Statistical analysis title	Analysis for change in acr
Statistical analysis description:	
All low values are assigned the value 0.00001 as per instructions	
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.87
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-0.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.286
upper limit	1.105
Variability estimate	Standard error of the mean
Dispersion value	0.592

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Until end of trial 23/01/2017	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	No coding performed
Dictionary version	0
Reporting groups	
Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Surgery	Additional description: Admitted for elective spinal surgery for spinal stenosis. Discharged on day 3 post admission on 30/07/16. Participant informed PI of date for elective surgery on 08/07/16 and of discharge on 05/08/16		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)		
Cardiac disorders			
Vasovagal fainting episode			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported