Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel-group trial of Vitamin D supplementation compared to placebo in people presenting with their First Episode of psychosis (DFEND) Neuroprotection Design

Summary

EudraCT number	2014-002639-32
Trial protocol	GB
Global end of trial date	20 December 2019

Results information

Result version number	v2 (current)
This version publication date	11 July 2021
First version publication date	10 February 2021
Version creation reason	• New data added to full data set • Correction of full data set • Changes to summary attachments Results delayed by COVID available to be posted
Summary attachment (see zip file)	Clinical Study report (DFEND Clinical Study Report v1.0 dated 29.04.2021 final.docx)

Trial information

Trial identification

Sponsor protocol code	3310

Additional study identifiers

ISRCTN number	ISRCTN12424842
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Dr Fiona Gaughran, Institute of Psychiatry, +44 2032286000, fiona.1.gaughran@kcl.ac.uk
Scientific contact	Dr Fiona Gaughran, Institute of Psychiatry, +44 2032286000, fiona.1.gaughran@kcl.ac.uk
Sponsor organisation name	South London and Maudsley NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 8AZ
Public contact	Dr Fiona Gaughran, Institute of Psychiatry, +44 2032286000, fiona.1.gaughran@kcl.ac.uk
Scientific contact	Dr Fiona Gaughran, Institute of Psychiatry, +44 2032286000, fiona.1.gaughran@kcl.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	20 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the addition of 120,000 IU monthly of vitamin D (cholecalciferol) supplement to standard treatments is more effective than placebo in improving outcomes (Positive And Negative Syndrome Scale Total score – PANSS) at six month follow-up in those with First Episode Psychosis.

Protection of trial subjects:

Patients are free to withdraw consent for study treatment and/or consent to participate in the study at any time and without the prejudice to further treatment. Patients who withdraw from study treatment, but are willing to continue to participate in the follow-up visits, should be followed according to the procedures outlined in the protocol. The role of the trial steering committee for this trial was to provide independent oversight of ethical and safety aspects of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 2016
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: 149
Worldwide total number of subjects	149
EEA total number of subjects	149

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)	149
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from 19th Jan 2016 to 14th June 2019 at 5 NHS sites within the English Mental Health Care System. Participants were recruited from two sources within the involved centres: community mental health services and inpatient services.

Pre-assignment

Screening details:

All patients within Early Intervention Services and First Episode Psychosis inpatient units who met the eligibility criteria were invited to participate in the study. Members of the research team regularly attended community team bases and wards to talk to staff and potentially interested patients.

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, Data analyst, Assessor

Blinding implementation details:

Blinded members of staff included all research team members at site level including chief investigator (CI), principal investigator (PI), researchers conducting participant follow ups and trial statisticians. Throughout the trial, no emergency unblinding occurred.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D

Arm description:

The IMP was given orally as a 6mL dose of liquid, via a syringe. This corresponded to 120,000 IU of vitamin D3. Placebo was administered the same way.

Arm type	Experimental
Investigational medicinal product name	Cholecalciferol
Investigational medicinal product code	
Other name	Vigantol Oil, Vitamin D3
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Cholecalciferol (vitamin D3), 120,000 IU per month (equivalent to 4,000 IU per day), was given orally as Vigantol® oil (by Merck GmbH) cholecalciferol dispersed in triglyceride oil as vehicle; containing 20,000 IU cholecalciferol per 1ml drop, and administered as 6mL given in a graduated oral syringe by a fully trained member of the research team for 6 months.

Arm title	Placebo

Arm description:

The comparator drug of Vigantol® oil will be achieved by using an organoleptically matched triglyceride oil (Miglyol® 812 oil) for the placebo.

Arm type	Placebo
Investigational medicinal product name	Miglyol® 812 oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Active and placebo treatment will be administered orally as 6mL given in a graduated oral syringe by a trained researcher once a month for 6 months.

Number of subjects in period 1	Vitamin D	Placebo
Started	74	75
Completed	50	54
Not completed	24	21
Consent withdrawn by subject	7	11
Physician decision	4	1
Lost to follow-up	10	6
moved out of area	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Vitamin D
Reporting group description:	
The IMP was given orally as a 6mL dose of liquid, via a syringe. This corresponded to 120,000 IU of vitamin D3. Placebo was administered the same way.	
Reporting group title	Placebo
Reporting group description:	
The comparator drug of Vigantol® oil will be achieved by using an organoleptically matched triglyceride oil (Miglyol® 812 oil) for the placebo.	

Reporting group values	Vitamin D	Placebo	Total
Number of subjects	74	75	149
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 of the study population			0
Age continuous			
Units: years			
arithmetic mean	27.76	28.39	
standard deviation	± 8.74	± 8.39	-
Gender categorical			
Units: Subjects			
Female	23	37	60
Male	51	38	89
Baseline CDS score			
Calgary Depression Scale (CDS) is a nine-item scale that assesses the level of depression, higher scores being worse. Scores are attributed by the researcher following an interview with the participant. There was one missing value in each of the trial arms.			
Units: score			
arithmetic mean	5.37	5.95	
standard deviation	± 5.26	± 5.24	-
Baseline GAF Disability score			
The GAF (Global Assessment of Functioning) has two scores (Disability and Symptoms) rated by a study researcher on a patient's functioning, scores range from 100 to 1 with lower scores being worse. There were no missing values for the baseline GAF scores.			
Units: score			
arithmetic mean	62.28	62.59	
standard deviation	± 14.52	± 16.87	-
Baseline GAF Symptom score			

Units: score			
arithmetic mean	61.51	62.77	
standard deviation	± 14.51	± 16.27	-
Baseline PANSS total score			
The Positive and Negative Syndrome Scale (PANSS) measures symptom severity of psychosis, with subscales measuring positive symptoms, negative symptoms and generally psychopathology. Lower scores indicate less severe symptoms, and better clinical outcome. There were no missing values for the baseline PANSS total score or subscores.			
Units: score			
arithmetic mean	56.5	57.28	
standard deviation	± 12.38	± 14.27	-

End points

End points reporting groups

Reporting group title	Vitamin D
Reporting group description:	
The IMP was given orally as a 6mL dose of liquid, via a syringe. This corresponded to 120,000 IU of vitamin D3. Placebo was administered the same way.	
Reporting group title	Placebo
Reporting group description:	
The comparator drug of Vigantol® oil will be achieved by using an organoleptically matched triglyceride oil (Miglyol® 812 oil) for the placebo.	

Primary: Month 6 PANSS total score

End point title	Month 6 PANSS total score
End point description:	
End point type	Primary
End point timeframe:	
The Positive and Negative Syndrome Scale (PANSS) measures symptom severity of psychosis, with subscales measuring positive symptoms, negative symptoms and generally psychopathology. Lower scores indicate less severe symptoms, and better clinical outcome.	

End point values	Vitamin D	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: score				
arithmetic mean (standard deviation)	55.88 (± 17.46)	53.04 (± 14.16)		

Statistical analyses

Statistical analysis title	Mean Difference (VitD – placebo)
Comparison groups	Vitamin D v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.981
upper limit	2.125

Variability estimate	Standard error of the mean
Dispersion value	2.294

Adverse events

Adverse events information	
Timeframe for reporting adverse events: IMP allocation to 28 days post last dose	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Vitamin D
Reporting group description: The IMP was given orally as a 6mL dose of liquid, via a syringe. This corresponded to 120,000 IU of vitamin D3. Placebo was administered the same way.	
Reporting group title	Placebo
Reporting group description: The comparator drug of Vigantol® oil will be achieved by using an organoleptically matched triglyceride oil (Miglyol® 812 oil) for the placebo.	

Serious adverse events	Vitamin D	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 74 (8.11%)	12 / 75 (16.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
acid reflux			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic behaviour	Additional description: psychotic exacerbation		
subjects affected / exposed	2 / 74 (2.70%)	8 / 75 (10.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

deterioration in mental health			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persecutory delusion			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive symptom	Additional description: DEPRESSIVE EPISODE WITH FEATURES OF PSYCHOSIS		
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, olfactory			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vitamin D	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 74 (39.19%)	37 / 75 (49.33%)	
General disorders and administration site conditions			
Fall			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
lack of motivation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
restless legs			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Immune system disorders			
Immunology test abnormal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	13 / 74 (17.57%)	4 / 75 (5.33%)	
occurrences (all)	13	4	
Psychiatric disorders			
Psychological disorder			
subjects affected / exposed	13 / 74 (17.57%)	21 / 75 (28.00%)	
occurrences (all)	13	21	
Investigations			
raised ALT & Albumin			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
high cholesterol			

subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
high triglycerides			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Blood neutrophil count decreased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	2 / 74 (2.70%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Nervous system disorders			
Neurological examination abnormal			
subjects affected / exposed	1 / 74 (1.35%)	3 / 75 (4.00%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Haematology test abnormal			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 74 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	14 / 74 (18.92%)	11 / 75 (14.67%)	
occurrences (all)	14	11	
Hepatobiliary disorders			
Hepatic disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Dermatologic examination abnormal			
subjects affected / exposed	1 / 74 (1.35%)	12 / 75 (16.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Urinary tract disorder			
subjects affected / exposed	1 / 74 (1.35%)	3 / 75 (4.00%)	
occurrences (all)	1	3	
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	2 / 74 (2.70%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	3 / 74 (4.05%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	0	
Wisdom teeth removal			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	Definition of First Episode Psychosis (FEP) changed from "within 6 months of presenting to services" to "within 3 years of presenting to services". Impact to inclusion criteria.
27 June 2017	Vitamin D supplement of 400 IU/day was allowed in both treatment arms.
07 September 2017	Inclusion age increased from 45 to 65 years. Removal of concomitant anticonvulsant therapy from exclusion criteria. Study length reduced from 12 months to 6 months. Change in SAE reporting so that hospitalisations for worsening of mental health symptoms would be recorded as SAEs but not reportable to Sponsor. Blood HCG sample was permitting for pregnancy testing if urine sample could not be provided. Definition of visit window was defined as -2/+2 weeks and 21 days in between doses.
10 July 2018	Time between doses increased to 24 days. Clarification of window for collection of final assessment -4/+6 weeks from Month 6 anchor date. Pregnancy test not required if medically sterile or post-menopause. Vitamin D levels will be sent to GP at the end of the study.
07 June 2019	Clarification that AEs were collected until 28-days after the last dose of IMP (if no dose at last visit then no follow-up is needed)

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/31907006