Clinical trial results:
Can Vitamin D supplementation improve Hepatitis C cure rates: A pilot multicentre randomised controlled clinical trial

Summary

EudraCT number	2013-003573-10
Trial protocol	GB
Global end of trial date	22 December 2015

Results information

Result version number	v1 (current)
This version publication date	13 May 2017
First version publication date	13 May 2017
Summary attachment (see zip file)	Summary results viaduct (ct_result_2013-003573-10 Viaduct Dillon.pdf)

Trial information

Trial identification

Sponsor protocol code	2012GA03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02053519
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor R&D number: 2012GA03

Notes:

Sponsors

Sponsor organisation name	University of Dundee
Sponsor organisation address	Ninewells Hospital, Dundee, United Kingdom, DD1 9SY
Public contact	Prof John Dillon, University of Dundee, 44 01382383017, j.f.dillon@dundee.ac.uk
Scientific contact	Prof John Dillon, University of Dundee, 44 01382383017, j.f.dillon@dundee.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	05 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2015
Global end of trial reached?	Yes
Global end of trial date	22 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to test if vitamin D supplementation improves the chances of standard treatment for HCV infection being effective. To test this we will measure if there is an improvement in the virologic response - ie the level of virus in the blood, 12 weeks after completion of treatment.

Protection of trial subjects:

Trial exclusion criteria were designed to minimize the risk of hypercalcemia or renal stones (know side effects of vitamin D therapy); drug exclusions were designed to minimize the risk of interactions with vitamin D.

Adverse events were sought at each clinic visit; the directly observed nature of the vitamin D administration once a month ensured close observation of participants throughout the trial.

Background therapy:

Standard HCV therapy was commenced 1-4 weeks after the first dose of vitamin D or placebo. Standard treatment for HCV is generally for 24 weeks. Some genotype 1 patients who do not respond to therapy at week 4 or 12 will have all anti-viral therapy stopped. Other genotype 1 patients who respond but do not become virus negative by 12 weeks of therapy will continue on a further 24 week course of standard therapy, total duration 48 weeks. Standard therapy for HCV genotype 1 patients changed as the trial commenced and some patients received sofosbuvir in addition to interferon for 12 weeks.

Evidence for comparator:

Placebo was selected (in addition to standard therapy) as the aim of the trial was to test efficacy of vitamin D in addition to standard therapy, rather than instead of standard therapy.

Actual start date of recruitment	01 November 2013
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: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	72
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from hepatitis C treatment services across multiple Scottish secondary care sites

Pre-assignment

Screening details:

At the screening visit all participants had their medical history taken and gave written informed consent. Confirmation of HCV diagnosis by viral genotype and viral load by PCR was taken from the last available values in the medical notes.

Period 1

Period 1 title	Randomised treatment (overall period)
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:

Matching IMP and placebo (base oil) were prepared by an independent provider (Tayside Pharmaceuticals) who dispensed identical bottles with no external indication of allocation group

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D3

Arm description:

Oral vitamin D3 100,000 units once per month

Arm type	Experimental
Investigational medicinal product name	Cholecalciferol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100,000 units once a month, given as 5mls of 20,000 units/ml product (Vigantol oil)

Arm title	Placebo

Arm description:

Matching placebo given once a month

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

Dosage and administration details:

5mls of matching placebo (Mygliol oil as used as base oil in Vigantol oil preparation) given once a month

Number of subjects in period 1	Vitamin D3	Placebo
Started	35	37
Completed	30	30
Not completed	5	7
Lost to follow-up	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Vitamin D3
Reporting group description:	
Oral vitamin D3 100,000 units once per month	
Reporting group title	Placebo
Reporting group description:	
Matching placebo given once a month	

Reporting group values	Vitamin D3	Placebo	Total
Number of subjects	35	37	72
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	42.5	41.7	
standard deviation	± 11.6	± 8.7	-
Gender categorical			
Units: Subjects			
Female	10	13	23
Male	25	24	49

End points

End points reporting groups

Reporting group title	Vitamin D3
Reporting group description:	
Oral vitamin D3 100,000 units once per month	
Reporting group title	Placebo
Reporting group description:	
Matching placebo given once a month	
Subject analysis set title	ITT analysis set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants with a value for the primary outcome (SVR12)	

Primary: SVR12 (sustained virologic response at 12 weeks)

End point title	SVR12 (sustained virologic response at 12 weeks)
End point description:	
Sustained virologic response 12 weeks after stopping treatment. Response = undetectable Hep C RNA at any point beyond 12 weeks post end of interferon-based treatment. Missing data analysed as treatment failure.	
End point type	Primary
End point timeframe:	
12 weeks after cessation of standard (interferon based) Hep C treatment	

End point values	Vitamin D3	Placebo	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	37	72	
Units: patients				
Treatment success	29	27	56	
Treatment failure	6	10	16	

Statistical analyses

Statistical analysis title	Adjusted odds ratio for treatment success
Comparison groups	Vitamin D3 v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	6.97

Secondary: Time to stopping standard treatment (adherence)

End point title	Time to stopping standard treatment (adherence)

End point description:

Time to stopping standard (interferon-based) treatment as a measure of adherence; comparison between vitamin D and placebo groups

End point type	Secondary

End point timeframe:

Baseline to 48 weeks

End point values	Vitamin D3	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: days				
median (inter-quartile range (Q1-Q3))	195 (112 to 270)	224 (119 to 303)		

Statistical analyses

Statistical analysis title	Hazard ratio-time to stopping standard treatment

Statistical analysis description:

Cox regression analysis

Comparison groups	Placebo v Vitamin D3
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.09

Secondary: 25-hydroxyvitamin D levels	
End point title	25-hydroxyvitamin D levels
End point description: Change from baseline averaged over follow up period	
End point type	Secondary
End point timeframe: Baseline to 48 weeks	

End point values	Vitamin D3	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: nmol/L				
arithmetic mean (standard deviation)	16.7 (± 39.5)	-7.9 (± 21.8)		

Statistical analyses

Statistical analysis title	Between group difference in 25OHD levels
Comparison groups	Vitamin D3 v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	24.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.2
upper limit	37.2

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening visit to 48 weeks (final visit)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18
Reporting groups	
Reporting group title	Vitamin D3
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	Vitamin D3	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	2 / 37 (5.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer	Additional description: Ulcer on leg		
subjects affected / exposed	0 / 35 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Intentional overdose	Additional description: Intentional heroin overdose		
subjects affected / exposed	0 / 35 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vitamin D3	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 35 (80.00%)	31 / 37 (83.78%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 35 (2.86%)	6 / 37 (16.22%)	
occurrences (all)	1	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 35 (17.14%)	8 / 37 (21.62%)	
occurrences (all)	6	9	
Vomiting			
subjects affected / exposed	3 / 35 (8.57%)	3 / 37 (8.11%)	
occurrences (all)	3	4	
Appetite disorder			
subjects affected / exposed	2 / 35 (5.71%)	3 / 37 (8.11%)	
occurrences (all)	2	3	
Throat irritation			
subjects affected / exposed	3 / 35 (8.57%)	2 / 37 (5.41%)	
occurrences (all)	3	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 35 (8.57%)	3 / 37 (8.11%)	
occurrences (all)	3	3	
Influenza-like illness			
subjects affected / exposed	2 / 35 (5.71%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Respiratory tract infection			
subjects affected / exposed	4 / 35 (11.43%)	1 / 37 (2.70%)	
occurrences (all)	8	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 35 (11.43%)	7 / 37 (18.92%)	
occurrences (all)	5	7	

Pruritis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5 4 / 35 (11.43%) 5	3 / 37 (8.11%) 3 2 / 37 (5.41%) 2	
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6	6 / 37 (16.22%) 6	
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 4	0 / 37 (0.00%) 0	
Metabolism and nutrition disorders Weight decreased subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	0 / 37 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2013	Revision of protocol to v2.0 with additional exclusion criteria added

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.

Recruited fewer participants than originally powered for. Changes in background therapy for hepatitis C mean results may not now be applicable to current standard of care. High cure rates in placebo group limit ability to detect treatment effect.

Notes: