Clinical trial results:
Efficacy of Vitamin D Supplementation in relapsing-remitting Multiple Sclerosis

Summary

EudraCT number	2011-002785-20
Trial protocol	DE
Global end of trial date	26 June 2017

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information

Trial identification

Sponsor protocol code	EVIDIMS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Lindenberger Weg 80, Berlin, Germany, 13125
Public contact	Herr PD Dr. med. Jan-Markus Dörr, Charité - Universitätsmedizin Berlin Campus Buch Experimental and Clinical Research Center (ECRC), 0049 30450660162, jan-markus.doerr@charite.de
Scientific contact	Herr Univ.-Prof. Dr. Friedemann Paul, Charité - Universitätsmedizin Berlin Campus Buch Experimental and Clinical Research Center (ECRC), 0049 30450639705, friedemann.paul@charite.de

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	26 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of Vitamin D supplementation in relapsing-remitting Multiple Sclerosis

Protection of trial subjects:

The study is approved by the local ethics committee and the German Competent Authority (Federal Institute for Drugs and Medical Devices) and is registered at both the European Union Drug Regulating Authorities . The study will be conducted in accordance to the Declaration of Helsinki in its currently applicable version, the guidelines of the International Conference on Harmonization of Good Clinical Practice (ICH-GCP), and the applicable German laws. All participants will be required to give informed written consent. The trial will be monitored according to ICH-GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2011
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	Germany: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	53
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Nevertheless, unforeseen recruitment difficulties such as the contemporaneous approval of oral MS drugs and a highly comparative environment with a large number of recruiting clinical trials may explain why, despite a fairly long recruitment period of 45 months, only 53 patients were randomized.

Pre-assignment

Screening details:

53 Patients were screened for eligibility

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Substantial efforts are made to maintain blinding: Since high-dose formulation (oil) does not match the low-dose formulation (tablet), patients in the high-dose arm will take 400 IU tablets in addition to 20.000 IU oil, whereas patients in the lowdose arm will receive an identical volume of placebo-oil in addition to a 400 IU tablet.

Arms

Are arms mutually exclusive?	Yes
Arm title	VD-high-dose Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Vigantol® Öl 20.000 I.E./ml COLECALCIFEROL
Investigational medicinal product code	SUB06794MIG
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

will receive 20.400 IU cholecalciferol orally every other day.
Since high-dose formulation (oil) does not match the low-dose formulation (tablet), patients in the high-dose arm will take 400 IU tablets in addition to 20.000 IU oil

Investigational medicinal product name	Dekristol® 400-Tabletten COLECALCIFEROL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

patients in the high-dose arm will take 400 IU tablets in addition to 20.000 IU oil

Arm title	VD-low-dose Group+PBO

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:
identical volume of placebo-oil in addition to a 400 IU tablet

Investigational medicinal product name	Dekristol® 400-Tabletten COLECALCIFEROL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
patients in the low-dose arm will take 400 IU tablets with placebo-oil

Number of subjects in period 1	VD-high-dose Group	VD-low-dose Group+PBO
Started	28	25
Completed	21	17
Not completed	7	8
Adverse event, non-fatal	1	1
Lost to follow-up	1	-
personal reasons	1	5
Protocol deviation	4	2

Baseline characteristics

Reporting groups	
Reporting group title	VD-high-dose Group
Reporting group description: -	
Reporting group title	VD-low-dose Group+PBO
Reporting group description: -	

Reporting group values	VD-high-dose Group	VD-low-dose Group+PBO	Total
Number of subjects	28	25	53
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41	45	
standard deviation	± 2.1	± 1.8	-
Gender categorical Units: Subjects			
Female	20	17	37
Male	8	8	16
Disease course			
RRMS: relapsing remitting MS; CIS: clinically isolated syndrome			
Units: Subjects			
RRMS	26	25	51
CIS	2	0	2
disease duration onset to screening Units: months			
arithmetic mean	97	125	
standard deviation	± 14.4	± 16.8	-
Mean BMI at screening			
BMI: body mass index;			
Units: Score			
arithmetic mean	27.2	25.5	
standard deviation	± 1.3	± 0.9	-
Mean EDSS at screening			
EDSS: Expanded Disability Status Scale			
Units: Score			
arithmetic mean	2.0	2.5	
full range (min-max)	0 to 5	0 to 6	-
Mean 25OH vitamin D serum level Units: (ng/ml			
arithmetic mean	18.8	17.8	
standard deviation	± 1.9	± 1.7	-
Mean T2w lesion count (n) Units: count			
arithmetic mean	52.6	76.1	

standard deviation	± 6.7	± 10.7	-
Mean T2w lesion volume Units: ml			
arithmetic mean	4.6	10.4	
standard deviation	± 0.9	± 1.9	-
Mean brain parenchymal fraction Units: ml			
arithmetic mean	1163.1	1121.3	
standard deviation	± 25.8	± 18.1	-
Mean thalamus volume Units: ml			
arithmetic mean	15.5	14.4	
standard deviation	± 0.4	± 0.4	-

End points

End points reporting groups

Reporting group title	VD-high-dose Group
Reporting group description: -	
Reporting group title	VD-low-dose Group+PBO
Reporting group description: -	

Primary: the number of new T2-weighted (T2w) hyperintense lesions

End point title	the number of new T2-weighted (T2w) hyperintense lesions
End point description:	
End point type	Primary
End point timeframe: after 18 months	

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: Count				
arithmetic mean (standard error)				
Mean T2w lesion change from baseline	53.4 (± 7.3) 1.3 (± 0.1)	84.1 (± 13.5) 2.1 (± 1.4)		

Statistical analyses

Statistical analysis title	T2w count after 18 months
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	T2w change from baseline
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	MANCOVA

Secondary: T2w lesion volume after 18 months

End point title	T2w lesion volume after 18 months

End point description:

End point type	Secondary

End point timeframe:
after 18 months

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: ml				
arithmetic mean (standard error)				
T2w lesion	4.6 (± 0.9)	10.4 (± 1.9)		

Statistical analyses

Statistical analysis title	T2w lesion volume after 18 months
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	T2w lesion volume change from baseline
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	MANCOVA

Secondary: brain parenchymal fraction after 18 months

End point title	brain parenchymal fraction after 18 months
End point description:	
End point type	Secondary
End point timeframe: after 18 months	

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: ml				
arithmetic mean (standard error)				
BPF	1167.7 (± 25.9)	1126.6 (± 20.7)		
change from baseline	-9.3 (± 3.7)	-7.3 (± 2.6)		

Statistical analyses

Statistical analysis title	BPF after 18 months
Comparison groups	VD-low-dose Group+PBO v VD-high-dose Group
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	BPF change from baseline
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	MANCOVA

Secondary: brain volume after 18 months

End point title	brain volume after 18 months

End point description:

End point type	Secondary
End point timeframe: after 18 months	

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: percent				
arithmetic mean (standard error)				
brain volume changes (%)	-0.61 (± 0.12)	-0.52 (± 0.1)		

Statistical analyses

Statistical analysis title	brain volume after 18 months
Comparison groups	VD-high-dose Group v VD-low-dose Group+PBO
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: thalamus volume after 18 months	
End point title	thalamus volume after 18 months
End point description:	

End point type	Secondary
End point timeframe: after months	

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: ml				
arithmetic mean (standard error)				
thalamus volume change from baseline	15.7 (± 0) 0.41 (± 0.6)	14.4 (± 0.5) 0.41 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: cumulative number of new gdþ lesions

End point title	cumulative number of new gdþ lesions

End point description:

End point type	Secondary

End point timeframe:

18 months

End point values	VD-high-dose Group	VD-low-dose Group+PBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	25		
Units: cumulative number				
number gd+ lesions (V0–V6)	2	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 18 months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	Own
Dictionary version	1
Reporting groups	
Reporting group title	Total AE from both Arms

Reporting group description: -

Serious adverse events	Total AE from both Arms		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Total AE from both Arms		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 53 (75.47%)		
Musculoskeletal and connective tissue disorders			
musculoskeletal complaints			
subjects affected / exposed	15 / 53 (28.30%)		
occurrences (all)	15		
Infections and infestations			
respiratory infections			
subjects affected / exposed	25 / 53 (47.17%)		
occurrences (all)	25		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2012	update protocol Version 1.2 (09/01/2012), change in interpretation of scientific documents, addition of a new site
25 November 2013	Change of principal investigator at an exsting site, addition of a new site
23 December 2013	update protocol Version 1.3 (20/12/2013), changes in conduct of trial - due to changes in manufacturing of Viganto Öl I.E./ ml -we had to adjust the amount of drops to achieved the required dosage
22 July 2015	Recruitment stop

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.

Finally, the rather small sample size may well account for the lack of differences in both study arms during therapy with a drug that significantly reduces relapses and MRI activity.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32047645