



Clinical trial results:

Vitamin D supplementation in cutaneous malignant melanoma outcome Summary

EudraCT number	2012-002125-30
Trial protocol	BE HU
Global end of trial date	25 July 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2024
First version publication date	11 October 2024

Trial information

Trial identification

Sponsor protocol code	2012LRDVDCM
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01748448
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZLeuven / KULeuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Dermatology clinical trials, Dermatology, 0032 16337950, dermatologie-admin@uzleuven.ac.be
Scientific contact	Dermatology clinical trials, Dermatology, 0032 16337950, dermatologie-admin@uzleuven.ac.be

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	27 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2022
Global end of trial reached?	Yes
Global end of trial date	25 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether vitamin D supplementation, in the follow up period after diagnosis and surgery of the primary tumor, has a protective effect on relapse of cutaneous malignant melanoma and whether this protective effect correlates with VDR immunoreactivity in the primary tumour.

Protection of trial subjects:

A DSMB Committee has analysed key safety aspects (safety parameters and adverse events) in regular intervals during the ongoing trial to ensure patient safety.

The DSMB was unblinded and composed of medical experts not involved in the study: a dermatologist, oncologist and statistician. They assessed the safety of patients based on the safety parameters and adverse events. In particular, at regular intervals an unblinded interim analysis was performed to assess the difference between the intervention arms and to exclude an increase in relapse rate in the vitamin D supplemented arm. No early stopping for efficacy was allowed.

Safety aspects:

- serum calcium, phosphorus, to detect for vitamin D intoxication (every 3 months)
- measurement of total WBC and differential (every 6 months) and a record of infection rate (every 3 months) to check for immunosuppressive effects
- Adverse clinical events

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2012
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	Hungary: 4
Country: Number of subjects enrolled	Belgium: 432
Worldwide total number of subjects	436
EEA total number of subjects	436

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)	321
From 65 to 84 years	115
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After diagnosis, staging and surgical treatment, and after obtaining written informed consent, patient will undergo screening at the investigational site to ensure that the patient meets all other in- and exclusion criteria. Written informed consent must be obtained from patients prior to any study specific procedure.

Pre-assignment

Screening details:

Screening phase: Patients are recruited at the Departments of Dermatology, Oncosurgery or Medical Oncology at the University Hospitals Leuven (Belgium), and other European academic sites. If all eligibility criteria are met, patients are then randomized to the treatment or control group. Randomisation is completed via IVRS.

Period 1

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

Blinding implementation details:

Vitamin D3 supplementation is given to the patients assigned to the treatment group and placebo to the control group in a double blind manner. The randomization schedule will be kept under closure at the data management centre. All other study staff members, dermatologists, trial nurses, and patients will be blinded to the treatment allocation. The DSMB members may be unblinded to assess the safety of the patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	D-Cure® (cholecalciferol)

Arm description:

Name investigational product: D-Cure® (amp. cholecalciferol 100.000 U.I./ml)
Content of 1 ml amp.: Cholecalciferol 100.000 U.I./ml -DL α -Tocopherol. acetat - Sorbitol. oleic. polyoxyaethylenat. - Aetherol. aurantii corticis dulcis - olie van olijfolie ad 1 ml
Administration route: orally

Arm type	Active comparator
Investigational medicinal product name	D-Cure® (amp. cholecalciferol 100.000 U.I./ml)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

D-Cure® amp. 100.000 U.I/ml
D-Cure® (oral ampoules) will be stored at room temperature, below 25 °C.
Administration route: orally

Arm title	Placebo: Oil
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Arm description:

Name investigational product: Oil
Oil will be used as matching placebo for vitamin D (cholecalciferol)
Composition: Tocopherol Acetate, sweet orange peel oil, Polyglyceryl oleate, olive oil refined ad 1ml
Administration route: orally

Arm type	Placebo
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Investigational medicinal product name	Placebo: Olive oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The -Olive oil (oral ampoules) will be stored at room temperature, below 25°C.

Administration route: orally

Number of subjects in period 1	D-Cure® (cholecalciferol)	Placebo: Oil
Started	218	218
Completed	216	217
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
personal	-	1

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

After the treatment period (in which the patients take study medication) (placebo or D-Cure), there is the follow-up period, no more study medication is taken, the study is still double-blind, and the patients are followed at the clinical department, Dermatology or Oncology, for relapse and/or death.

Arms

Arm title	Follow up
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Arm description:

After the treatment period (in which the patients take study medication, placebo or D-Cure), there is the follow-up period, no more study-medication is taken, the study is still double-blind, and the patients are followed at the clinical department, Dermatology or Oncology, for relapse and/or death.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Follow up
Started	433
Completed	433

Baseline characteristics

Reporting groups

Reporting group title	D-Cure® (cholecalciferol)
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Reporting group description:

Name investigational product: D-Cure® (amp. cholecalciferol 100.000 U.I./ml)

Content of 1 ml amp.: Cholecalciferol 100.000 U.I./ml -DL α -Tocopherol. acetat – Sorbitol. oleic. polyoxyaethylenat. - Aetherol. aurantii corticis dulcis - olie van olijfolie ad 1 ml

Administration route: orally

Reporting group title	Placebo: Oil
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Reporting group description:

Name investigational product: Oil

Oil will be used as matching placebo for vitamin D (cholecalciferol)

Composition: Tocopherol Acetate, sweet orange peel oil, Polyglyceryl oleate, olive oil refined ad 1ml

Administration route: orally

Reporting group values	D-Cure® (cholecalciferol)	Placebo: Oil	Total
Number of subjects	218	218	436
Age categorical			
Units: Subjects			
Adults (18-64 years)	157	164	321
From 65-84 years	61	54	115
Age continuous			
Units: years			
median	54.9	55.0	
standard deviation	± 13.12	± 13.27	-
Gender categorical			
Units: Subjects			
Female	112	125	237
Male	106	93	199
Current smoking			
Units: Subjects			
No	99	76	175
Yes	33	37	70
Never smoked	85	105	190
unknown	1	0	1
Education (highest level)			
Units: Subjects			
Primary	9	8	17
Secondary school	75	68	143
Vocational training	43	40	83
Vocational university	62	59	121
University graduated	27	42	69
Other	1	1	2
unknown	1	0	1
Naevus Phenotype_Number of benign naevi (>2mm)			
Units: Subjects			
<25	93	91	184

25-49	63	49	112
50-100	37	44	81
>100	23	34	57
unknown	2	0	2
Naevus Phenotype_Actinic Keratosis Units: Subjects			
Yes	23	26	49
No or unknown	195	192	387
Naevus Phenotype_Ephilides (freckles) on the face Units: Subjects			
yes	45	35	80
no or unknown	173	183	356
Naevus Phenotype_Idiopathic guttate hypomelanosis (legs and/or arms) Units: Subjects			
yes	30	24	54
no or unknown	188	194	382
Laboratory investigations_Serum phosphate Units: Subjects			
Not done	1	1	2
Within normal range	197	196	393
Outside normal range: not clinically significant	20	21	41
Pathology_Time of diagnosis Units: Subjects			
Newly diagnosed	53	53	106
Diagnosis <= 6 Months Ago	105	102	207
Diagnosis 6<-12 Months Ago	60	63	123
Pathology_Histological subtype Units: Subjects			
Nodular melanoma	38	29	67
Superficial spreading melanoma	115	142	257
Acrolentigineus melanoma	8	6	14
Lentigo maligna melanoma	7	5	12
Unknown	23	21	44
Other	27	15	42
Pathology_Clark Units: Subjects			
Level II	9	10	19
Level III	78	72	150
Level IV	107	114	221
Level V	15	12	27
Unknown	9	10	19
Pathology_Ulceration Units: Subjects			
Yes	42	40	82
No or unknown	176	178	354
Pathology_Mitoses Units: Subjects			
Yes	189	187	376

No or unknown	29	31	60
Pathology_VDR immuno-reactivity in the primary tumor Units: Subjects			
nul	2	3	5
1+	62	57	119
2+	75	73	148
3+	20	19	39
Failed	6	11	17
Not done	53	55	108
Metastasis and Staging_Sentinel Node Biopsy Units: Subjects			
Yes	177	182	359
No or unknown	41	36	77
Metastasis and Staging_Metastasis in Lymph Nodes Units: Subjects			
Yes	34	33	67
No or Unknown	184	185	369
Metastasis and Staging_Staging AJCC 8th edition Units: Subjects			
IA	24	26	50
IB	101	108	209
IIA	29	30	59
IIB	18	14	32
IIC	10	6	16
IIIA	14	10	24
IIIB	9	8	17
IIIC	10	14	24
IIID	0	1	1
IV	1	0	1
Unknown	2	1	3
Body Mass Index (BMI) Units: kg/m²			
arithmetic mean	27	27	
standard deviation	± 5	± 4	-
Laboratory investigations_Vitamin-D Units: ng/ml			
median	24	21	
inter-quartile range (Q1-Q3)	18 to 30	16 to 29	-
Laboratory investigations_Vitamin-D Units: ng/ml			
arithmetic mean	24	23	
standard deviation	± 9	± 9	-
Laboratory investigations_Serum calcium Units: mg/dL			
arithmetic mean	9	10	
standard deviation	± 1	± 1	-
Laboratory investigations_Serum calcium			

Units: mg/dL median inter-quartile range (Q1-Q3)	10 9 to 10	10 9 to 10	-
Pathology_Breslow Units: mm arithmetic mean standard deviation	2 ± 2	2 ± 2	-
Pathology_Breslow Units: mm median inter-quartile range (Q1-Q3)	1 1 to 2	1 1 to 2	-

End points

End points reporting groups

Reporting group title	D-Cure® (cholecalciferol)
Reporting group description:	
Name investigational product: D-Cure® (amp. cholecalciferol 100.000 U.I./ml)	
Content of 1 ml amp.: Cholecalciferol 100.000 U.I./ml -DL α -Tocopherol. acetat - Sorbitol. oleic. polyoxyaethylenat. - Aetherol. aurantii corticis dulcis - olie van olijfolie ad 1 ml	
Administration route: orally	
Reporting group title	Placebo: Oil
Reporting group description:	
Name investigational product: Oil	
Oil will be used as matching placebo for vitamin D (cholecalciferol)	
Composition: Tocopherol Acetate, sweet orange peel oil, Polyglyceryl oleate, olive oil refined ad 1ml	
Administration route: orally	
Reporting group title	Follow up
Reporting group description:	
After the treatment period (in which the patients take study medication, placebo or D-Cure), there is the follow-up period, no more study-medication is taken, the study is still double-blind, and the patients are followed at the clinical department, Dermatology or Oncology, for relapse and/or death.	

Primary: Relapse-Free Survival_Death or relapse

End point title	Relapse-Free Survival_Death or relapse
End point description:	
The difference in relapse-free survival will be compared between the two treatment groups by means of a Cox proportional hazards model for interval censored data stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago). The model will be fitted using PROC ICPHREG using the EMCIM algorithm and the baseline hazards will be estimated using cubic splines. The best fitting model using 2 to 5 degrees of freedom will be chosen based on Akaike Information Criterion (AIC). The hazard ratio with a 95% confidence interval and corresponding p-value will be reported.	
It will be verified whether the treatment effect is stratum dependent. This will be done by analysing each stratum separately and performing a Chi-square test to compare the treatment effect between the 3 strata. If found significant, the strata will be reported separately.	
End point type	Primary
End point timeframe:	
Treatment period and follow up period	

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: number				
Death or Relapse	41	32		

Statistical analyses

Statistical analysis title	Primary endpoint: relapse free survival
Statistical analysis description:	
A comparison between the 2 treatment groups was conducted using a COX proportional hazards model stratified by time since diagnosis. Tied survival times were managed using Efron's method.	
Comparison groups	D-Cure® (cholecalciferol) v Placebo: Oil
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Fisher exact
Parameter estimate	Cox proportional hazard
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.03

Primary: Relapse-Free Survival_Estimated Event Rates

End point title	Relapse-Free Survival_Estimated Event Rates
End point description:	
<p>The difference in relapse-free survival will be compared between the two treatment groups by means of a Cox proportional hazards model for interval censored data stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago). The model will be fitted using PROC ICPHREG using the EMCIM algorithm and the baseline hazards will be estimated using cubic splines. The best fitting model using 2 to 5 degrees of freedom will be chosen based on Akaike Information Criterion (AIC). The hazard ratio with a 95% confidence interval and corresponding p-value will be reported.</p> <p>It will be verified whether the treatment effect is stratum dependent. This will be done by analysing each stratum separately and performing a Chi-square test to compare the treatment effect between the 3 strata. If found significant, the strata will be reported separately.</p>	
End point type	Primary
End point timeframe:	
Overall period and follow up period	

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: Percentage				
number (confidence interval 95%)				
At 12 Months	4.68 (2.54 to 8.52)	7.24 (4.42 to 11.72)		
At 24 Months	12.53 (8.64 to 18.01)	9.34 (6.06 to 14.27)		
At 36 Months	14.93 (10.60 to 20.83)	11.76 (7.95 to 17.21)		
At 72 Months	26.51 (19.37 to 35.64)	20.70 (14.26 to 29.52)		

Statistical analyses

Statistical analysis title	Primary endpoint: relapse free survival
Statistical analysis description: A comparison between the 2 treatment groups was conducted using a COX proportional hazards model stratified by time since diagnosis. Tied survival times were managed using Efron's method.	
Comparison groups	D-Cure® (cholecalciferol) v Placebo: Oil
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Fisher exact
Parameter estimate	Cox proportional hazard
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.03

Secondary: Melanoma-Related Death_melanoma/non-melanoma related death

End point title	Melanoma-Related Death_melanoma/non-melanoma related death
End point description: Melanoma related death will be analysed by a Fine and Gray model (Fine and Gray, 1999) stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago) and in which non melanoma-related death is treated as a competing risk. The hazard ratio with a 95% confidence interval and corresponding p-value will be reported. In case the relation to melanoma is unknown, it will be analysed as related. A sensitivity analysis for which the assumption is made that the death is not related will be performed.	
End point type	Secondary
End point timeframe: Treatment period and follow up period	

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: number				
Melanoma-Related Death	10	11		
Non-Melanoma Related Death	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Melanoma-Related Death_Estimated Event Rates

End point title	Melanoma-Related Death_Estimated Event Rates
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End point description:

Melanoma related death will be analysed by a Fine and Gray model (Fine and Gray, 1999) stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago) and in which non melanoma-related death is treated as a competing risk. The hazard ratio with a 95

End point type	Secondary
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End point timeframe:

Treatment period and follow-up period

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: percent				
number (confidence interval 95%)				
At 12.0 Months	0.5 (0.0 to 2.5)	0.5 (0.0 to 2.5)		
At 24.0 Months	2.6 (1.0 to 5.6)	2.1 (0.7 to 4.9)		
At 36.0 Months	3.7 (1.6 to 7.2)	3.2 (1.3 to 6.6)		
At 72.0 Months	7.0 (3.3 to 12.6)	8.1 (4.0 to 14.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival_ All-Cause death

End point title	Overall Survival_ All-Cause death
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End point description:

Overall survival will be analysed using a Cox proportional hazards model for right censored data stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago). The hazard ratio with a 95% confidence interval and corresponding p-value will be reported.

It will be verified whether the treatment effect is stratum dependent. This will be done by analysing each stratum separately and performing a Chi-square test to compare the treatment effect between the 3 strata. If found significant, the strata will be reported separately.

End point type	Secondary
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End point timeframe:

Treatment period and follow-up period

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: number				
All-Cause Death	13	13		
All-Cause Death Within 72 Months	13	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival_ Estimated Event Rates

End point title	Overall Survival_ Estimated Event Rates
End point description:	
Overall survival will be analysed using a Cox proportional hazards model for right censored data stratified for time since diagnosis (3 strata: 0, 6 or 12 months ago). The hazard ratio with a 95% confidence interval and corresponding p-value will be reported. It will be verified whether the treatment effect is stratum dependent. This will be done by analysing each stratum separately and performing a Chi-square test to compare the treatment effect between the 3 strata. If found significant, the strata will be reported separately.	
End point type	Secondary
End point timeframe:	
Treatment period and follow-up period	

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	218		
Units: percent				
number (confidence interval 95%)				
At 12 Months	0.48 (0.07 to 3.35)	0.49 (0.07 to 3.44)		
At 24 Months	2.59 (1.08 to 6.11)	2.08 (0.78 to 5.44)		
At 36 Months	3.74 (1.80 to 7.70)	3.23 (1.46 to 7.06)		
At 72 Months	11.83 (6.54 to 20.88)	9.50 (5.19 to 17.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of 25(OH)D3_Summary over Time (mean)

End point title	Evolution of 25(OH)D3_Summary over Time (mean)
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End point description:

The evolution of 25(OH)D3 serum levels will be described descriptively over time.

In addition, the influence of a 10-fold genetic SNP on the baseline Vitamine D level will be investigated by means of an analysis of variance (ANOVA).

For those patients randomized to the Vitamin D group, the changes in 25(OH)D3 serum level from baseline to 6 and 12 months will be compared for each genetic snip. A random intercept model with the 6- and 12-months measurement as response and the baseline value, time (6 or 12 months), a genetic snip and the interaction between time and snip as covariate will be fitted to the data. The change from baseline at 6 and 12 months by SNP will be reported with a 95% CI.

End point type	Secondary
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End point timeframe:

From baseline untill End of Study = Treatment period

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218 ^[1]	218 ^[2]		
Units: ng/ml				
arithmetic mean (standard deviation)				
Baseline	24 (± 9)	23 (± 9)		
Month 3	40 (± 10)	21 (± 6)		
Month 6	43 (± 11)	23 (± 9)		
Month 9	38 (± 12)	25 (± 11)		
Month 12	44 (± 11)	24 (± 9)		
Month 15	39 (± 12)	21 (± 7)		
Month 18	44 (± 11)	24 (± 11)		
Month 21	40 (± 9)	27 (± 8)		
Month 24	42 (± 11)	24 (± 9)		
Month 27	44 (± 9)	21 (± 8)		
Month 30	44 (± 12)	27 (± 8)		
Month 33	40 (± 9)	29 (± 5)		
Month 36	40 (± 12)	25 (± 7)		
Month 39	38 (± 6)	21 (± 8)		
Study End	43 (± 12)	27 (± 9)		

Notes:

[1] - Number of subjects is different from each time point.

[2] - Number of subjects is different from each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of 25(OH)D3_Summary over Time (median)

End point title	Evolution of 25(OH)D3_Summary over Time (median)
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End point description:

The evolution of 25(OH)D3 serum levels will be described descriptively over time.

In addition, the influence of a 10-fold genetic SNP on the baseline Vitamine D level will be investigated by means of an analysis of variance (ANOVA).

For those patients randomized to the Vitamin D group, the changes in 25(OH)D3 serum level from baseline to 6 and 12 months will be compared for each genetic snip. A random intercept model with the 6- and 12-months measurement as response and the baseline value, time (6 or 12 months), a genetic snip and the interaction between time and snip as covariate will be fitted to the data. The change from baseline at 6 and 12 months by SNP will be reported with a 95% CI.

End point type	Secondary
End point timeframe:	
From baseline untill End of Study = Treatment period	

End point values	D-Cure® (cholecalciferol)	Placebo: Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218 ^[3]	218 ^[4]		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))				
Baseline	24 (18 to 30)	21 (16 to 29)		
Month 3	38 (33 to 51)	20 (18 to 23)		
Month 6	41 (36 to 49)	24 (17 to 30)		
Month 9	37 (27 to 46)	21 (17 to 34)		
Month 12	44 (36 to 51)	22 (18 to 28)		
Month 15	38 (31 to 42)	21 (16 to 26)		
Month 18	44 (36 to 50)	23 (18 to 30)		
Month 21	38 (32 to 47)	25 (23 to 26)		
Month 24	42 (35 to 50)	24 (18 to 29)		
Month 27	40 (38 to 51)	18 (17 to 30)		
Month 30	46 (34 to 53)	26 (20 to 32)		
Month 33	39 (34 to 44)	29 (26 to 32)		
Month 36	39 (31 to 48)	24 (20 to 29)		
Month 39	36 (34 to 41)	21 (15 to 26)		
Study End	42 (34 to 50)	27 (20 to 33)		

Notes:

[3] - Number of subjects is different in all timepoints

[4] - Number of subjects is different in all timepoints

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In this study, the collection period for adverse events starts at randomisation and ends when the patient completes the study or at premature termination. (untill end of overall period)

Adverse event reporting additional description:

The investigator will use the following terms to assess the severity of the adverse event: mild, moderate, severe

The investigator will use the following causality terms to assess the relationship of the adverse event or clinical efficacy event to the use of the investigational medicinal product: Reasonable causal relationship or not.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Adverse events_Control group
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Reporting group description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

Reporting group title	Adverse events_Vit-D group
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Reporting group description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious adverse events	Adverse events_Control group	Adverse events_Vit-D group	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 218 (15.14%)	28 / 218 (12.84%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	5 / 218 (2.29%)	6 / 218 (2.75%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Vascular disorders			

subjects affected / exposed	1 / 218 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	6 / 218 (2.75%)	6 / 218 (2.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	3 / 218 (1.38%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 218 (0.46%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	2 / 218 (0.92%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 218 (0.46%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	2 / 218 (0.92%)	4 / 218 (1.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	0 / 218 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 218 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 218 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	5 / 218 (2.29%)	3 / 218 (1.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 218 (0.46%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	2 / 218 (0.92%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 218 (0.92%)	3 / 218 (1.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Endocrine disorders			
subjects affected / exposed	0 / 218 (0.00%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	4 / 218 (1.83%)	4 / 218 (1.83%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	1 / 218 (0.46%)	3 / 218 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adverse events_Control group	Adverse events_Vit-D group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	178 / 218 (81.65%)	180 / 218 (82.57%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	11 / 218 (5.05%)	18 / 218 (8.26%)	
occurrences (all)	13	24	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 218 (0.46%)	2 / 218 (0.92%)	
occurrences (all)	1	2	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	16 / 218 (7.34%)	14 / 218 (6.42%)	
occurrences (all)	17	16	
Pregnancy, puerperium and perinatal conditions			

Pregnancy, puerperium and perinatal conditions subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	0 / 218 (0.00%) 0	
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	32 / 218 (14.68%) 44	36 / 218 (16.51%) 47	
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	6 / 218 (2.75%) 6	6 / 218 (2.75%) 6	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	46 / 218 (21.10%) 63	29 / 218 (13.30%) 42	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	1 / 218 (0.46%) 1	
Product issues Product issues subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	42 / 218 (19.27%) 44	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	7 / 218 (3.21%) 7	9 / 218 (4.13%) 13	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	7 / 218 (3.21%) 7	15 / 218 (6.88%) 16	
Blood and lymphatic system disorders Blood and lymphatic system disorders			

subjects affected / exposed occurrences (all)	3 / 218 (1.38%) 3	8 / 218 (3.67%) 10	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	4 / 218 (1.83%) 5	7 / 218 (3.21%) 7	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	5 / 218 (2.29%) 5	9 / 218 (4.13%) 9	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	29 / 218 (13.30%) 38	33 / 218 (15.14%) 36	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	2 / 218 (0.92%) 2	5 / 218 (2.29%) 6	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	22 / 218 (10.09%) 36	35 / 218 (16.06%) 57	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	13 / 218 (5.96%) 19	17 / 218 (7.80%) 20	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	99 / 218 (45.41%) 132	44 / 218 (20.18%) 50	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	37 / 218 (16.97%) 51	39 / 218 (17.89%) 67	
Infections and infestations			

Infections and infestations subjects affected / exposed occurrences (all)	55 / 218 (25.23%) 82	57 / 218 (26.15%) 72	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	1 / 218 (0.46%) 1	2 / 218 (0.92%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2013	Protocol, version 2, 22-03-2013: Adjust in/exclusion criteria
13 September 2013	Protocol, version 3, 20-08-2013: Addition of new centers
23 December 2015	Protocol, version 4, 25-11-2015: Change of in-and exclusion criteria, reporting certain abnormal lab values as an adverse event
19 October 2017	Protocol, version 5, 27-09-2017: Medication change: from 4 oral syringes of 25000 units to 1 ampoule of 100000 units
26 March 2018	Protocol, version 6, 20-02-2018: Adjustment of Adverse events
25 April 2019	Protocol, version 7, 19-03-2019: Change of address and addition of additional financing
17 May 2021	Protocol, version 8, 05-01-2021: Information about SNPs analysis in lab of VIB

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/38913652>

<http://www.ncbi.nlm.nih.gov/pubmed/28835228>

<http://www.ncbi.nlm.nih.gov/pubmed/35312026>