Clinical trial results:
Vitamin D supplementation to palliative cancer patients - A double blind, randomised controlled trial

Summary

EudraCT number	2017-000268-14
Trial protocol	SE
Global end of trial date	21 May 2021

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021
Summary attachment (see zip file)	Clinical Study Report for Palliative D (Slutrapport Palliative D_210520_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	170113

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Stockholms Läns Landsting
Sponsor organisation address	Bergtallsvägen 12, Stockholm, Sweden, 12559
Public contact	Linda Björkhem-Bergman, ASIH Stockholm Södra, Långbro Park, linda.bjorkhem-bergman@ki.se
Scientific contact	Linda Björkhem-Bergman, ASIH Stockholm Södra, Långbro Park, linda.bjorkhem-bergman@ki.se

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	21 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2021
Global end of trial reached?	Yes
Global end of trial date	21 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to test the hypothesis vitamin D supplementation for 12 weeks reduces opioid consumption.

Protection of trial subjects:

All collected data was coded with study numbers

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2017
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	Sweden: 244
Worldwide total number of subjects	244
EEA total number of subjects	244

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)	87
From 65 to 84 years	143
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

'Palliative-D' was a multicenter, double-blind parallel group, 1:1, randomized, placebo-controlled trial performed at three palliative care facilities in Stockholm, Sweden; ASIH Stockholm Södra, ASIH Stockholm Norr and ASIH Stockholms Sjukhem.

Pre-assignment

Screening details:

Included patients were admitted to one of the three recruiting palliative care facilities, ≥18 years old, had advanced and/or metastatic cancer in palliative phase (any type of cancer), a life expectancy of at least three months as assessed by one of the three study physician and 25-OHD ≤50 nmol/L. Ongoing oncological treatment was allowed.

Period 1

Period 1 title	Nov 2017 - June 2020 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Trial masking for patients, trial staff and care providers continued until data had been analysed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D

Arm description:

Patients were randomly assigned 1:1 to vitamin D3 oil drops (colour and taste matched) 4000 IU/day or placebo (oil drops) for 12 weeks, dispensed in identical, sequentially numbered bottles. Randomization was performed using a computer-generated randomization list to generate a permutated block randomization with a block size of four. Randomization was not stratified. Trial masking for patients, trial staff and care providers continued until data had been analysed. Detremin 20 000 IU/ml (cholecalciferol solved in Miglyol oil) and placebo (Miglyol oil) were prepared according to Good Manufacturing Practice by Nextpharma. Eurofins LC2, a centralized randomization unit, was responsible for labelling, blinding, and randomization. Detremin was provided from Renapharma Sweden, and placebo was from Nextpharma, France.

Arm type	Active comparator
Investigational medicinal product name	Detremin
Investigational medicinal product code	
Other name	cholecalciferol solved in Miglyol oil
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Patients were randomly assigned 1:1 to vitamin D3 oil drops (colour and taste matched) 4000 IU/day or placebo (oil drops) for 12 weeks, dispensed in identical, sequentially numbered bottles. Detremin 20 000 IU/ml (cholecalciferol solved in Miglyol oil) and placebo (Miglyol oil) were prepared according to Good Manufacturing Practice by Nextpharma. Eurofins LC2, a centralized randomization unit, was responsible for labelling, blinding, and randomization. Detremin was provided from Renapharma Sweden, and placebo was from Nextpharma, France.

Arm title	Placebo

Arm description:

Patients were randomly assigned 1:1 to vitamin D3 oil drops (colour and taste matched) 4000 IU/day or placebo (oil drops) for 12 weeks, dispensed in identical, sequentially numbered bottles. Randomization was performed using a computer-generated randomization list to generate a permutated block randomization with a block size of four. Randomization was not stratified. Trial masking for

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Arm type	Placebo
Investigational medicinal product name	Detremin
Investigational medicinal product code	
Other name	cholecalciferol solved in Miglyol oil
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

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Number of subjects in period 1	Vitamin D	Placebo
Started	121	123
Completed	67	83
Not completed	54	40
Death due to cancer	36	24
Consent withdrawn by subject	9	8
Adverse event, non-fatal	2	4
Protocol deviation	7	4

Baseline characteristics

Reporting groups

Reporting group title	Nov 2017 - June 2020

Reporting group description: -

Reporting group values	Nov 2017 - June 2020	Total	
Number of subjects	244	244	
Age categorical			
ITT-population, median age and IQR: 68 (61-75)			
Units: Subjects			
Above 18 years	244	244	
Age continuous			
Units: years			
median	68		
inter-quartile range (Q1-Q3)	61 to 75	-	
Gender categorical			
49% male			
Units: Subjects			
Female	124	124	
Male	120	120	

Subject analysis sets

Subject analysis set title	Primary outcome ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

244 patients were included in the ITT-analysis, which was based on 769 observations and 4 time-points over 12 weeks. Groups were well balanced at baseline (Table 1). The ITT-analysis did not show a significant difference between the slopes: beta -0.60 (95%CI -1.21; 0.02; p=0.06) and in the adjusted analysis: beta -0.59 (95%CI -1.20 to 0.03; p=0.06)

Subject analysis set title	Primary outcome PP
Subject analysis set type	Per protocol

Subject analysis set description:

In the PP-analysis (n=150), based on 450 observations, the vitamin D-group had significantly less increase of opioid doses during the study period compared to the placebo-group; beta -0.56 (95%CI -1.07; -0.05; p=0.03) in both the unadjusted and adjusted analysis, i.e. 0.56 µg less fentanyl/h and week with vitamin D treatment and corresponding to 6.72 ug/h after 12 weeks.

Reporting group values	Primary outcome ITT	Primary outcome PP	
Number of subjects	244	150	
Age categorical			
ITT-population, median age and IQR: 68 (61-75)			
Units: Subjects			
Above 18 years	244	150	
Age continuous			
Units: years			
median	68	68	
inter-quartile range (Q1-Q3)	61 to 75	61 to 75	

Gender categorical			
49% male			
Units: Subjects			
Female	124	76	
Male	120	74	

End points

End points reporting groups

Reporting group title	Vitamin D

Reporting group description:

Patients were randomly assigned 1:1 to vitamin D3 oil drops (colour and taste matched) 4000 IU/day or placebo (oil drops) for 12 weeks, dispensed in identical, sequentially numbered bottles. Randomization was performed using a computer-generated randomization list to generate a permutated block randomization with a block size of four. Randomization was not stratified. Trial masking for patients, trial staff and care providers continued until data had been analysed. Detremin 20 000 IU/ml (cholecalciferol solved in Miglyol oil) and placebo (Miglyol oil) were prepared according to Good Manufacturing Practice by Nextpharma. Eurofins LC2, a centralized randomization unit, was responsible for labelling, blinding, and randomization. Detremin was provided from Renapharma Sweden, and placebo was from Nextpharma, France.

Reporting group title	Placebo

Reporting group description:

Patients were randomly assigned 1:1 to vitamin D3 oil drops (colour and taste matched) 4000 IU/day or placebo (oil drops) for 12 weeks, dispensed in identical, sequentially numbered bottles. Randomization was performed using a computer-generated randomization list to generate a permutated block randomization with a block size of four. Randomization was not stratified. Trial masking for patients, trial staff and care providers continued until data had been analysed. Detremin 20 000 IU/ml (cholecalciferol solved in Miglyol oil) and placebo (Miglyol oil) were prepared according to Good Manufacturing Practice by Nextpharma. Eurofins LC2, a centralized randomization unit, was responsible for labelling, blinding, and randomization. Detremin was provided from Renapharma Sweden, and placebo was from Nextpharma, France.

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Subject analysis set title	Primary outcome PP
Subject analysis set type	Per protocol

Subject analysis set description:

In the PP-analysis (n=150), based on 450 observations, the vitamin D-group had significantly less increase of opioid doses during the study period compared to the placebo-group; beta -0.56 (95%CI -1.07; -0.05; p=0.03) in both the unadjusted and adjusted analysis, i.e. 0.56 µg less fentanyl/h and week with vitamin D treatment and corresponding to 6.72 ug/h after 12 weeks.

Primary: Decline in opioid doses

End point title	Decline in opioid doses

End point description:

Mean difference in change in long-acting opioid dose between the treatment arms, measured as fentanyl ug/hour during 12 weeks, based on 4 time-points: 0, 4, 8 and 12 weeks, and adjusted for baseline opioid-values. Values are presented as beta coefficinet and 95%CI.

End point type	Primary

End point timeframe:

12 weeks

End point values	Vitamin D	Placebo	Primary outcome ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	67[1]	83[2]	67[3]	
Units: ug/h				
number (confidence interval 95%)	-0.56 (-1.07 to -0.05)	0 (0 to 0)	-0.60 (-1.21 to 0.02)	

Notes:

[1] - PP analysis, beta coeffienct on the differance between the two treatment arms

[2] - PP

[3] - PP analysis, beta coefficent bewteen the two treatment arms

Statistical analyses

Statistical analysis title	Linear mixed effect regression

Statistical analysis description:

Primary analysis was done using linear mixed effect regression using information from three time points: 4, 8 and 12 weeks, adjusting for the baseline value.

Comparison groups	Vitamin D v Primary outcome ITT
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Nov 2017 to June 2020

Adverse event reporting additional description:

According to the study protocol, only GI-symptoms, increase in creatinine levels, hypercalcemia and renal failure needed to be recorded as adverse events. Data on this was collected at baseline and after 4, 8 and 12 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1.0

Reporting groups

Reporting group title	Vitamin D
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Vitamin D	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	
number of deaths (all causes)	26	24	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	
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: 1 %

Non-serious adverse events	Vitamin D	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 121 (4.13%)	4 / 123 (3.25%)	
Gastrointestinal disorders			
diarrhoea, nausea			
subjects affected / exposed	2 / 121 (1.65%)	1 / 123 (0.81%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			

Dyspnea subjects affected / exposed occurrences (all)	0 / 121 (0.00%) 5	1 / 123 (0.81%) 4	
Renal and urinary disorders hypercalcemia or increase in creatinine subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 5	2 / 123 (1.63%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2019	The exclusion criteria were changed from exclusion of patients on any type of vitamin D treatment or supplementation to allowing recruitment of patients on daily doses of vitamin D up to 400 IE/day. The change was made since large number of patients met this exclusion criterion and since this dose was not considered to affect the endpoints. 2) We added eGFR < 30 ml/h as an exclusion criterion for safety reasons.

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/32936046