



## Clinical trial results:

**A phase II, randomised, double-blind, and parallel study to estimate the dose-response of vitamin D supplementation in chronic kidney disease patients with secondary hyperparathyroidism and vitamin D deficiency.**

### Summary

EudraCT number	2019-000640-10
Trial protocol	BG
Global end of trial date	18 June 2020

### Results information

Result version number	v1 (current)
This version publication date	02 July 2021
First version publication date	02 July 2021

### Trial information

#### Trial identification

Sponsor protocol code	GPR-II-18-1
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Laboratoires SMB S.A.
Sponsor organisation address	26-28, rue de la Pastorale, Brussels, Belgium, 1080
Public contact	CLINICAL DEPARTMENT, LABORATOIRES SMB S.A, 32 2411 48 28, dptclinique@smb.be
Scientific contact	CLINICAL DEPARTMENT, LABORATOIRES SMB S.A, 32 2411 48 28, dptclinique@smb.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	03 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2020
Global end of trial reached?	Yes
Global end of trial date	18 June 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To estimate the dose-response on iPTH and related markers of vitamin D3 in chronic kidney disease patients (CKD stage 3) with secondary hyperparathyroidism and vitamin D deficiency.

Protection of trial subjects:

For this study, no particular measure was taken to protect the trial patients. The study treatment (Cholecalciferol/ vitamin D) was already on the European market and then were well known by the most of participating patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2019
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	Bulgaria: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	50
From 65 to 84 years	45
85 years and over	5

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in four sites in Bulgaria. The recruitment was adequate to meet the target of 100 patients. After the screening visit, the patients were randomized in one of the four groups of treatments. The study extended over 12 weeks of supplementation followed by a final visit 2 weeks after the last administration of study treatment.

### Pre-assignment

Screening details:

- Obtain signed ICF
- Obtain demo data
- Perform a medical history & physical examination
- Take vital signs
- Review prior/concomitant medications
- Perform laboratory evaluation & pregnancy test
- Review inclusion/exclusion criteria
- Schedule the randomisation visit

### 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, Monitor, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group 1 : 25.000 IU/mL per week

Arm description:

1 ampoule of cholecalciferol 25.000 IU/mL + 3 ampoules of placebo taken once a week during 12 weeks (total dose: 300.000 IU/mL)

Arm type	Experimental
Investigational medicinal product name	D-CURA 1 ml ampoule of 25.000 IU/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

One ampoule of 25.000 IU/mL was taken every week during 12 weeks (+ 3 placebo ampoules/week). The ampoules of placebo were given to maintain the blind between treatment groups.

<b>Arm title</b>	Group 2 : 50.000 IU/ml per week
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Arm description:

2 ampoules of cholecalciferol 25.000 IU/mL + 2 ampoules of placebo taken once a week during 12 weeks (total dose: 600.000 IU/mL)

Arm type	Experimental
Investigational medicinal product name	D-CURA 1 ml ampoule of 25.000 IU/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Two ampoules of 25.000 IU/mL were taken every week during 12 weeks (+ 2 placebo ampoules/week). The ampoules of placebo were given to maintain the blind between treatment groups.

<b>Arm title</b>	Group 3 : 75.000 IU/ml per week
Arm description: 3 ampoules of cholecalciferol 25.000 IU/mL + 1 ampoule of placebo taken once a week during 12 weeks (total dose: 900.000 IU/mL)	
Arm type	Experimental
Investigational medicinal product name	D-CURA 1 ml ampoule of 25.000 IU/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

**Dosage and administration details:**

Three ampoules of 25.000 IU/mL were taken every week during 12 weeks (+ 1 placebo ampoules/week).

The ampoules of placebo were given to maintain the blind between treatment groups.

<b>Arm title</b>	Group 4 : 100.000 IU/ml per week
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**Arm description:**

4 ampoules of cholecalciferol 25.000 IU/mL taken once a week during 12 weeks (total dose: 1.200,000 IU/mL)

Arm type	Experimental
Investigational medicinal product name	D-CURA 1 ml ampoule of 25.000 IU/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

**Dosage and administration details:**

Four ampoules of 25.000 IU/mL were taken every week during 12 weeks.

<b>Number of subjects in period 1</b>	Group 1 : 25.000 IU/mL per week	Group 2 : 50.000 IU/ml per week	Group 3 : 75.000 IU/ml per week
Started	25	25	25
Completed	25	24	24
Not completed	0	1	1
Adverse event, serious fatal	-	-	-
Fear of COVID-19	-	-	-
Consent withdrawn by subject	-	1	1

<b>Number of subjects in period 1</b>	Group 4 : 100.000 IU/ml per week
Started	25
Completed	23
Not completed	2
Adverse event, serious fatal	1
Fear of COVID-19	1
Consent withdrawn by subject	-



## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	100	100	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	50	50	
From 65-84 years	45	45	
85 years and over	5	5	
Age continuous			
Units: years			
arithmetic mean	64.5		
standard deviation	± 12.9	-	
Gender categorical			
Units: Subjects			
Female	42	42	
Male	58	58	

## End points

### End points reporting groups

Reporting group title	Group 1 : 25.000 IU/mL per week
Reporting group description: 1 ampoule of cholecalciferol 25.000 IU/mL + 3 ampoules of placebo taken once a week during 12 weeks (total dose: 300.000 IU/mL)	
Reporting group title	Group 2 : 50.000 IU/ml per week
Reporting group description: 2 ampoules of cholecalciferol 25.000 IU/mL + 2 ampoules of placebo taken once a week during 12 weeks (total dose: 600.000 IU/mL)	
Reporting group title	Group 3 : 75.000 IU/ml per week
Reporting group description: 3 ampoules of cholecalciferol 25.000 IU/mL + 1 ampoule of placebo taken once a week during 12 weeks (total dose: 900.000 IU/mL)	
Reporting group title	Group 4 : 100.000 IU/ml per week
Reporting group description: 4 ampoules of cholecalciferol 25.000 IU/mL taken once a week during 12 weeks (total dose: 1.200,000 IU/mL)	

### Primary: Change from baseline to week 12 in iPTH

End point title	Change from baseline to week 12 in iPTH
End point description:	
End point type	Primary
End point timeframe: Baseline (week 0) and Week 12	

End point values	Group 1 : 25.000 IU/mL per week	Group 2 : 50.000 IU/ml per week	Group 3 : 75.000 IU/ml per week	Group 4 : 100.000 IU/ml per week
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	24	23
Units: pg/mL				
least squares mean (confidence interval 95%)	-29.7 (-43.6 to -12.4)	-15.3 (-27.7 to -0.9)	-30.2 (-42.4 to -15.5)	-19.2 (-38.9 to 6.7)

### Statistical analyses

Statistical analysis title	Mixed model
Comparison groups	Group 1 : 25.000 IU/mL per week v Group 2 : 50.000 IU/ml per week v Group 3 : 75.000 IU/ml per week v Group 4 : 100.000 IU/ml per week

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

### Secondary: Change from baseline to week 12 in 25(OH)D3

End point title	Change from baseline to week 12 in 25(OH)D3
End point description:	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) and week 12	

End point values	Group 1 : 25.000 IU/mL per week	Group 2 : 50.000 IU/ml per week	Group 3 : 75.000 IU/ml per week	Group 4 : 100.000 IU/ml per week
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	24	23
Units: ng/mL				
least squares mean (standard error)	22.66 (± 3.498)	34.83 (± 5.027)	33.58 (± 5.634)	34.85 (± 5.199)

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The AEs were recorded during the entire study period.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Group 1 : 25.000 IU/mL per week
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Reporting group description:

1 ampoule of cholecalciferol 25.000 IU/mL + 3 ampoules of placebo taken once a week during 12 weeks (total dose: 300.000 IU/mL)

Reporting group title	Group 2 : 50.000 IU/ml per week
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Reporting group description:

2 ampoules of cholecalciferol 25.000 IU/mL + 2 ampoules of placebo taken once a week during 12 weeks (total dose: 600.000 IU/mL)

Reporting group title	Group 3 : 75.000 IU/ml per week
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Reporting group description:

3 ampoules of cholecalciferol 25.000 IU/mL + 1 ampoule of placebo taken once a week during 12 weeks (total dose: 900.000 IU/mL)

Reporting group title	Group 4 : 100.000 IU/ml per week
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Reporting group description:

4 ampoules of cholecalciferol 25.000 IU/mL taken once a week during 12 weeks (total dose: 1.200,000 IU/mL)

Serious adverse events	Group 1 : 25.000 IU/mL per week	Group 2 : 50.000 IU/ml per week	Group 3 : 75.000 IU/ml per week
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction caused by artery thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Group 4 : 100.000 IU/ml per week		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction caused by artery thrombosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Group 1 : 25.000 IU/mL per week	Group 2 : 50.000 IU/ml per week	Group 3 : 75.000 IU/ml per week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	2 / 25 (8.00%)	3 / 25 (12.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	2 / 25 (8.00%)
occurrences (all)	3	2	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1

<b>Non-serious adverse events</b>	Group 4 : 100.000 IU/ml per week		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	6		

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported