CONFIDENTIAL

CLINICAL REPORT SUMMARY

1. TITLE PAGE

Clinical Report No.:	Final version	**Protocol No.:**	D-CURE-IV-12-2
		EudraCT No.:	**2012-004917-14**
Date of Issue:	16/12/2013		
Study Title:	**A PHASE IV, RANDOMISED, DOUBLE-BLINDED, PARALLEL STUDY TO ESTIMATE THE DOSE-RESPONSE OF VITAMIN D (D-CURE®) SUPPLEMENTATION ON THE 25-HYDROXYVITAMIN D SERUM CONCENTRATION IN PATIENTS WITH VITAMIN D DEFICIENCY**		
Drug Name:	D-CURE®		
Indication / Purpose:	Patients with vitamin D deficiency		
Methodology:	Interventional, randomised, parallel, double-blinded study		
Drug Development Phase:	Phase IV		
Country:	Belgium		
Coordinating Investigator:	Dr Bernard Jandrain ATC SA CHU de Liège - Unité de Pharmacologie clinique 4000 Liège, Belgium		
First Patient First Visit:	12/12/2012		
Last Patient Last Visit:	03/05/2013		
Sponsor:	Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels, Belgium		

2. SYNOPSIS

Name of Sponsor/Company: Laboratoires SMB S.A.	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: D-CURE®		
Name of Active Ingredient: Cholecalciferol		

Title of Study:

A PHASE IV, RANDOMISED, DOUBLE-BLINDED, PARALLEL STUDY TO ESTIMATE THE DOSE-RESPONSE OF VITAMIN D (D-CURE®) SUPPLEMENTATION ON THE 25-HYDROXYVITAMIN D SERUM CONCENTRATION IN PATIENTS WITH VITAMIN D DEFICIENCY.

Study Center/Investigator:

One site in Belgium. The principal investigator was Dr Bernard Jandrain.

Publication (Reference):

Not applicable.

Study Period:	**Phase of Development:**
12 December 2012 (First Patient First Visit) 03 May 2013 (Last Patient Last Visit)	Phase IV

Objective:

To estimate the dose-response effect and determine an adapted supplementation of vitamin D (D-CURE®) in patients with deficiency in vitamin D concentration.

Methodology:

Phase IV, interventional, randomised, parallel, double-blinded study.

Number of Patients (Planned, Consented, Randomized and Analyzed):

Planned: 200 patients screened; 150 patients randomised (50 patients in each treatment group).

Screened: 196 patients screened

Randomized: 150 patients randomized (50 patients in each treatment group). All randomized patients received at least one treatment intake.

Completed: 148 patients completed the study (50 patients from the D-CURE 100 000 IU group, 49 patients from the D-CURE 200 000 IU group and 49 patients from the D-CURE 400 000 IU group).

Safety and ITT efficacy analysis: 150 patients (50 patients from the D-CURE 100 000 IU group, 50 patients from the D-CURE 200 000 IU group and 50 patients from the D-CURE 400 000 IU group).

PP analysis: 143 patients (48 patients from the D-CURE 100 000 IU group, 46 patients from the D-CURE 200 000 IU group and 49 patients from the D-CURE 400 000 IU group).

Diagnosis and Main Criteria for Inclusion:

Men and women aged over 18 years with vitamin D concentration ≥5 ng/mL and ≤20 ng/mL and BMI between 18 and 30 kg/m² inclusive.

Test Product, Dose and Mode of Administration, batch number:

D-CURE® 1 mL ampoule for oral use containing 25 000 IU/mL of vitamin D3 (cholecalciferol / batch number: GM12-038/R631) taken according the following scheme:

- **Group 1: 100 000 IU**

2 ampoules of D-CURE® taken at week 0 followed by 1 ampoule at week 4 and 8.
6 ampoules of placebo taken at week 0 followed by 3 ampoules at week 4 and 8.

- **Group 2: 200 000 IU**

4 ampoules of D-CURE® taken at week 0 followed by 2 ampoules at week 4 and 8.
4 ampoules of placebo taken at week 0 followed by 2 ampoules at week 4 and 8.

- **Group 3: 400 000 IU**

8 ampoules of D-CURE® taken at week 0 followed by 4 ampoules at week 4 and 8.

Placebo ampoules were given to maintain the blind between each treatment groups (batch number: GM12-

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040/R632). The treatment was to be taken with liquid (water or orange juice).

Duration of Treatment:

After being screened for the study, patients were randomised in the study for a period of 12 weeks during which they received the treatment according to the randomisation scheme.

Criteria for Evaluation:

❑ **Primary endpoint:**

- Mean change from baseline to week 12 (W12) in the 25-hydroxyvitamin D serum concentration.

❑ **Other efficacy parameters:**

- Percentage of patients reaching 25-hydroxyvitamin D serum concentrations superior to 20 ng/mL at the end of study (W12)
- Percentage of patients reaching 25-hydroxyvitamin D serum concentrations superior to 30 ng/mL at the end of the study (W12)
- Time to raise the 25-hydroxyvitamin D serum concentration up to 20 ng/mL
- Time to raise the 25-hydroxyvitamin D serum concentration up to 30 ng/mL

❑ **Safety parameters:**

- Adverse events (AEs)
- Physical examination
- Vital signs
- Laboratory data
- Withdrawals or drop-out rate

Statistical Methods:

Missing value after W4 (visit 3) were replaced by the last available observation (Last Observation Carried Forward). Baseline was measured at W0 (visit 2).

❑ **Descriptive statistics:**

Results are expressed as mean±SD for continuous variable and number (percentage) for categorical variables.

❑ **Comparisons of baseline characteristics:**

An ANOVA for the main baseline characteristics was performed to detect any global effect between the 3 treatment groups; a Cochran-Mantel-Haenszel test was used for categorical or binomial baseline characteristics.

❑ **Efficacy analysis:**

The main efficacy analysis was conducted in the Intent-To-Treat (ITT) population subset. The effect of treatment dose on change in vitamin D concentration was tested in a mixed model with baseline and treatment dose as fixed factors. Since dose in group 3 was two-times the dose in group 2 and 4 times the dose in group 1, the treatment dose was replaced by z= (log(dose)-log(100000))/log(2). To deal with multiple comparisons, comparisons were adjusted by the Bonferoni method. Type 1 error rate was set at 0.05. Estimates and two-sided confidence intervals were derived from the mixed model. Same models applied for changes between baseline and W4 or W8. The evolution of vitamin D concentration over time according to treatment groups was analyzed in a mixed model for repeated measures (time effect, z effect, time*z interaction effect). Modeling of change in vitamin D concentration according to treatment groups used a linear regression model. After having checked the adequacy of the linear regression model, a mixed model was built with dose and baseline as fixed effects. Predicted values were derived from the model and plotted against dose along with a two-sided 95% confidence interval. Same models were built for change between baseline and W4 or W8. Time to raise 25-OH vitamin D serum concentrations > 20 ng/mL (and respectively 30 ng/mL) was estimated using the Kaplan Meier's estimator.

❑ **Safety analysis:**

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The safety analysis was conducted in the safety population subset. The safety profile of the D-CURE® (including AEs and laboratory results) was described over the study.

Summary - Conclusions:

Efficacy Results:

The study demonstrated a dose-response relationship between the 3 groups, with increases in 25(OH)D levels proportionate to the dose administered. Mean increases in 25(OH)D levels were 7.92±0.87 ng/mL, 13.04±0.87 ng/mL and 20.18±0.86 ng/mL, respectively, for 100 000 IU, 200 000 IU and 400 000 IU after 12 weeks of supplementation. All contrasts examining between-group differences were highly significant ($p<0.0001$). 25-OH vitamin D level changed with time ($p<0.0001$) over the 12-week study period and evolution was different between groups ($p<0.0001$ for time*group interaction). Regression models showed that the relationship between dose of D-CURE® and 25-OH vitamin D blood level was almost linear (since the coefficient attributed to the quadratic term was very low). Treatment target of 20 ng/mL for 25-OH vitamin D was reached as soon as W8 in 98% of patients receiving 400 000 IU of D-CURE®. By contrast only 52% and 84% of patients receiving 100 000 IU or 200 000 IU achieved the treatment target of 20 ng/mL. Fewer patients achieved the target of 30 ng/mL: 64%, 24% and 4% of patients receiving 400 000 IU, 200 000 IU and 100 000 IU, respectively.

Safety Results:

D-CURE® appeared to be well tolerated. 46% to 54% of patients reported at least one adverse event during the 12-week study. All except two were of mild to moderate intensity and none was related to the study drug. One serious AE (suicide attempt) occurred during the study and was considered not related to the study drug. No change in haematological and biochemistry parameters was noticed during the study. No patient presented with a 25-OH vitamin D serum concentration exceeding 100 ng/mL over the study. SBP significantly decreased during the study with the three dosing schedules of D-CURE® and heart rate significantly decreased in patients from the 100 000 IU and 200 000 IU groups. DBP remained unchanged.

Conclusion:

Comparing the three dosing schedules

- 50 000 IU at W0, followed by 25 000 IU at weeks 4 and 8 (i.e. a global dose do 100 000 IU)
- 100 000 IU at W0, followed by 50 000 IU at weeks 4 and 8 (i.e. a global dose do 200 000 IU)
- 200 000 IU at W0, followed by 100 000 IU at weeks 4 and 8 (i.e. a global dose do 400 000 IU)

a dose-response was demonstrated between vitamin D administration and plasma levels. Serum concentration of 25(OH)D >20 ng/ml was obtained for all subjects (98%) in the group receiving the high dose of vitamin D only (100 000 IU per month). Starting the treatment with a high loading dose allows faster correction of the vitamin D deficiency.