CONFIDENTIAL

CLINICAL STUDY REPORT SYNOPSIS

1. TITLE PAGE

Clinical Report No.:	2.0	**Protocol No.:**	D-CURE-IV-14-1
		EudraCT No.:	2014-003779-48
Date of Issue:	December 02, 2015		
Study Title:	**A phase IV, randomised, cross-over study to estimate the influence of food on the 25-hydroxyvitamin D3 serum level after vitamin D3 (D-CURE®) supplementation**		
Drug Name:	D-CURE®		
Indication / Purpose:	To determine whether administration of vitamin D_3 (D-CURE®) with food improve the absorption and increase serum levels of 25-hydroxyvitamin D_3.		
Methodology:	Interventional, open, randomised, 2-treatment, 2-period, cross-over study		
Drug Development Phase:	IV		
Country:	Belgium		
Coordinating Investigator:	Dr Bernard Jandrain, M.D. Advanced Technology Corporation (ATC) SA Unité de Pharmacologie clinique CHU de Liège, B35, Tour 2, Niveau -2E 4000 – Liège, Belgium		
First Subject First Visit:	October 22, 2014		
Last Subject Last Visit:	March 23, 2015		
Sponsor Signatory:	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, cross-over study to estimate the influence of food on the 25-hydroxyvitamin D_3 serum level after vitamin D_3 (D-CURE®) supplementation

Study Center/Investigator:

The study was conducted in 1 center in Belgium. Dr. Bernard Jandrain was the principal investigator.

Publication (Reference):

Not applicable

Study Period:	**Phase of Development:**
22 October 2014 (First Subject First Visit) - 23 March 2015 (Last Subject Last Visit)	Phase IV

Objectives:

To determine whether administration of vitamin D_3 (D-CURE®) with food improve the absorption and increase serum levels of 25-hydroxyvitamin D_3.

Methodology:

- Phase IV, interventional, open, randomised, 2-treatment, 2-period, cross-over study

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

- Planned: 88 subjects to randomize
- Entered: 105 screened subjects and 88 randomized subjects (2 groups of 44 subjects)
- Completed: 88 subjects
- Analyzed:
  - SA set: 88 subjects
  - ITT set: 88 subjects
  - PP set: 83 subjects

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

Subjects had to satisfy the following criteria before entering the study:

1) Male and female aged from 18 to 55 years inclusive;
2) Caucasian

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3) Having a 25(OH)D_3 ≥10 ng/ml and ≤ 20 ng/ml at the screening visit.
4) Presenting a body mass index (BMI) between 18 and 25 kg/m² inclusive;
5) Able to comply with all study procedures;
6) Provide written informed consent to participate in the study, indicated by a personal signature and date on the subject consent form;
7) If the volunteer was female and of childbearing potential, she had to use an efficient mean of birth control (IUD, OCS, spermicide + condom), as determined by the investigator and had to provide a negative blood pregnancy test at the screening visit.

Exclusion criteria

Subjects who met any of the following criteria were excluded from participating in the study:

1) Evidence of any unstable or untreated clinically significant immunological, neoplastic, endocrine, haematological, hepatic, renal, gastrointestinal, neurological or psychiatric abnormalities or medical disease;
2) Past or current granulomatosis (Besnier-Boek-Schaumann disease), sarcoïdosis, urinary lithiasis, renal insufficiency, cardiac disease, cancer, osteomalacia;
3) Abnormal digestive functions (obstructive jaundice, pancreatic insufficiency, cystic fibrosis, celiac disease, etc);
4) Abnormal thyroid function confirmed by an abnormal TSH;
5) Subjects who had a serum creatinine > 150 µmol/L (corresponding to 17 mg/L) at screening;
6) Subjects who had an albumin corrected serum calcium > 2.65 mmol/L (corresponding to 10.6 mg/dl) at screening;
7) Subjects known to have, or at risk of contracting, human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
8) Use of any vitamin D supplement alone or in association within 2 months before the screening visit and during the study;
9) UV light solarium use 2 months before the screening visit and during the study;
10) Travelling to regions with high UVB incidence in the last 2 months and during the study;
11) History of drug and/or alcohol abuse;
12) Use of any prohibited medication as detailed in the concomitant medication section;
13) Participation in any other clinical trial within one month of the screening visit;

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14) Hypersensitivity to the active ingredient and/or excipients of D-CURE®.
15) Presence of any other condition or illness, which, in the opinion of the investigator, could have interfered with optimal participation in the study.

Test Product, Dose and Mode of Administration, Batch Number:

D-CURE® 1 ml ampoule for oral use containing 25,000 IU/ml of vitamin D_3 (cholecalciferol) (Batch number: GM14-055)

Two ampoules of D-CURE® (total 50,000 IU) were taken at the beginning of each treatment period (day 1) in either a fasting condition (Treatment 2) or after a standardized high fat breakfast (Treatment 1) according to the randomization list.

Duration of Treatment:

- **Screening period:** 1 to 28 days prior to the randomisation.
- **Treatment periods:** 2 periods of 60±3 days. The subjects received two ampoules of D-CURE® (each containing 25,000 IU/ml) on the first day of each of the two periods.

Criteria for Evaluation:

Primary efficacy assessment:

- Mean change in serum 25(OH)D_3 levels (from baseline to D14).

Secondary efficacy assessments:

- Serum 25(OH)D_3 levels at day 1, 3, 5, 7, 14±1, 30±2 and 60±3 of each period
- Change in serum 25(OH)D_3 levels from baseline to day 3, 5, 7, 14±1, 30±2 and 60±3 of each period
- AUC of serum 25(OH)D_3 level (minus baseline) against time

Safety assessment:

- AEs
- Changes in vital signs
- Changes in weight and BMI

Statistical Methods:

The statistical analysis was performed using the 9.4 SAS software (SAS Institute, Cary, NC,

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USA).

Populations:

The efficacy analysis was conducted for the ITT set. Analysis of safety was done with the SA dataset.

Safety Analysis (SA):	All subjects who were randomized and received at least one dose of study medication
Intent To Treat (ITT):	All subjects of the SA set with at least one measurement of the primary variable after drug administration of each period. Drop-outs prior to Period II could not be analyzed for efficacy and were excluded from this subset
Per Protocol (PP):	All subjects of the ITT set, completing all study visits and for whom no major protocol deviations were documented

General considerations

- Baseline values: serum 25(OH)D_3 level measured on D1 of each period

Efficacy analysis

Primary analysis: mean change in serum 25(OH)D_3 levels from baseline to D14

- One-sided test with a type I error rate set at 0.025
- Null hypothesis: the concomitant intake of food with administration of D-CURE® has no effect on 25(OH) D serum level at D14 after a single intake of D-CURE®

Secondary analyses:

- Mixed models:
  - Fixed factor: administration of food concomitantly with D-CURE® intake, period, sequence
  - Random factors: baseline (D1 predose), BMI and subject*sequence interaction (carry-over effect)

Safety analysis

Descriptive statistics were used for the safety analysis.

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Summary - Conclusions:

Efficacy Results:

After a single administration of 50.000 IU/ml of vitamin D_3 under fasting conditions or with a high fat meal, the serum concentration of 25(OH) D_3 rapidly increased (25.1±4.3 versus 25.1±4.9 ng/ml), reached a plateau from D3 to D14 (25.6±4.3 versus 25.7±4.6 ng/ml) and slowly decreased until D60. After 60 days, the 25(OH) D_3 serum level returned to a level close to the baseline value measured before vitamin D administration (17.2±3.6 versus 17.8±4.0 ng/ml). The evolution of 25(OH)D_3 serum concentration measured over the study was similar between the fasting and the high fat periods and no effect of conditions of intake was observed.

In both conditions, the 25(OH) D_3 serum level was significantly higher than the baseline value 3 days after administration and remained significantly higher during the first month. The increment was the same when the vitamin D_3 was taken in fasting conditions or with a high fat meal (8.0±2.8 versus 8.5±3.3 ng/ml).

Similarly, no effect of fasting versus fat conditions was observed for the Area Under the Curve calculated after 30 and 60 days; the estimated difference between means being not significant.

Results were confirmed in two robustness analyses differing by the imputation methods of missing data and in the per-protocol subset.

Table 1. Change D1-D14 in 25(OH)D_3 –ITT

		Fasting	High fat
D1 predose (ng/ml)	m±S	17.1±4.0	16.6±4.2
D14 (ng/ml)	m±SD	25.6±4.3	25.7±4.6
Change (ng/ml)	m±SD	8.5±3.8	9.1±4.1
Food effect	P	0.068	
Estimated means	m±SE	9.03±0.41	9.65±0.40
Difference	m±SE	0.61±0.41	
	97.5% one-sided CI	[-0.20 ; + ∞]	

Evolution of 25(OH)D_3 against time - ITT

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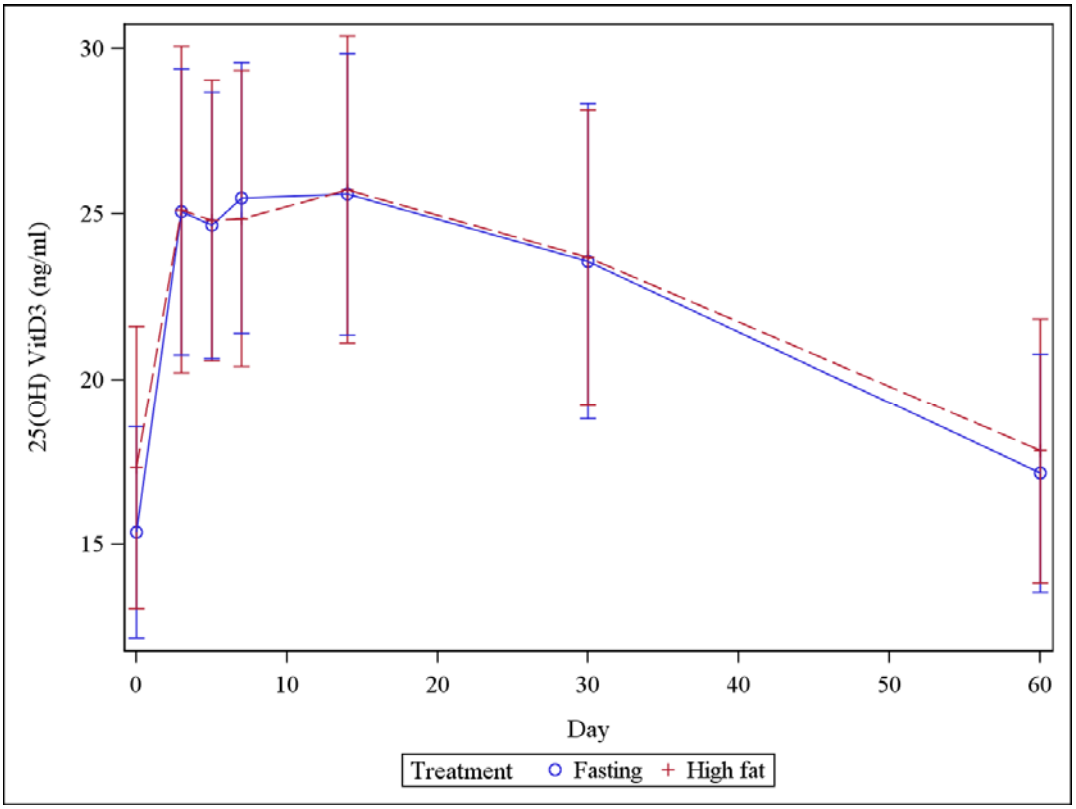

Safety Results:

No treatment-related adverse event was reported during the study confirming the good safety profile of D-CURE® whatever the conditions of intake (fasting or high fat conditions). No adverse events were considered as treatment-related, they were all of mild or moderate intensity and no serious adverse events were reported. Vital signs remained unchanged. The maximal 25(OH) D_3 serum level observed during the study was respectively of 44 ng/ml in fasting conditions and 40 ng/ml with a high fat meal confirming that at the dosage strength of 50.000 IU, D-CURE® provides concentrations far from 150 ng/ml, generally considered as the potentially "toxic" limit.

Conclusion:

This cross-over study has demonstrated that the vitamin D_3 absorption taken from D-CURE® (oral ampoule containing an oily solution of vitamin D_3) was not influenced by the presence or absence of a meal.